The American Journal of Medicine

April 1947

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The American Journal of Medicine

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1. Batterman, R. C.: Arch. Int. Med. 71:345, 1943.
2. Batterman, R. C.: Connecticut M. J. 8:13, 1944.

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The American Journal of Medicine

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Supplementing the diet with *both* vitamins and minerals is clearly logical because of the now confirmed nutritional concepts originally advanced by Dr. Casimir Funk in 1936:

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General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

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BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

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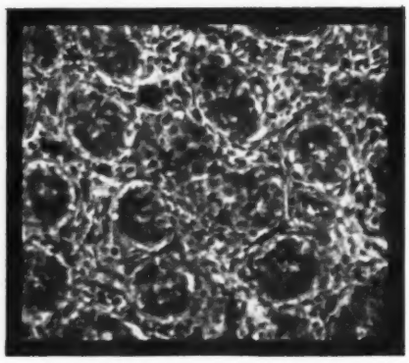
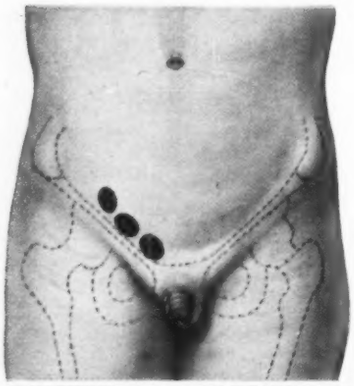


Photomicrograph of undescended human testicle. Transection of tubules. Masson III stain.

Complete information on Perandren and Metandren Linguets will be sent to any physician on request. Write Professional Service Dept.

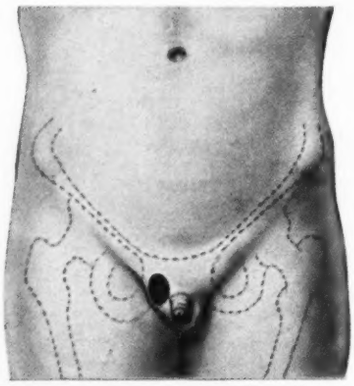
1. Thompson, W. O.: J.A.M.A., 132: 185, 1946.

MALPOSITION OF THE TESTICLE



Right abdominal testicle. Three positions of the undescended testicle in the abdomen.

Right pubo-scrotal testicle. Position of the undescended testicle in the pubo-scrotal region.



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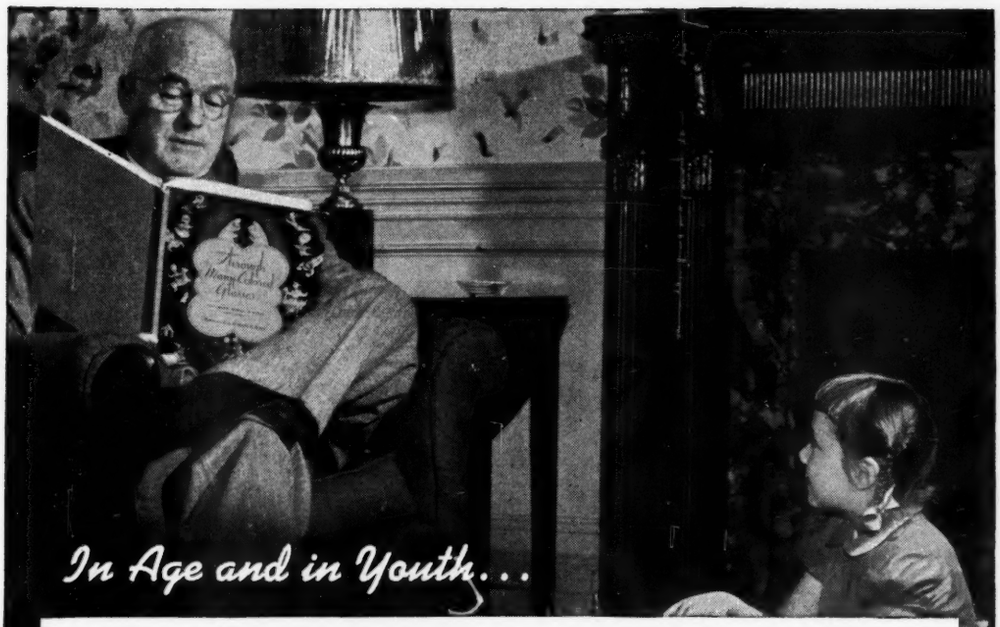

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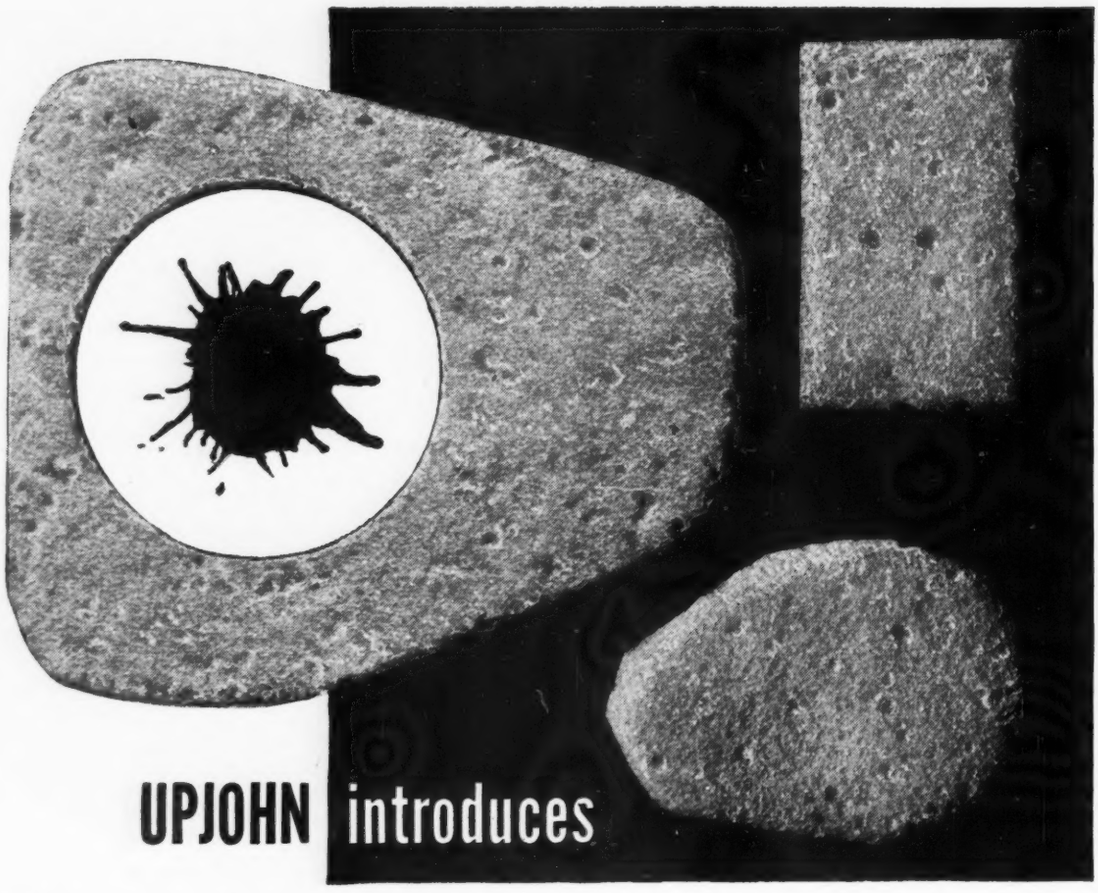

UPJOHN introduces

the newest advance in the control of bleeding

The development of Gelfoam* by the Upjohn research laboratories marks a new advance in hemostasis. Gelfoam is a readily absorbable, easily cut and molded gelatin sponge which may be used with or without thrombin and may be left in situ without fear of tissue reactions. Gelfoam makes readily available biochemical hemostasis to simplify the clearing of oozing surfaces, the control of capillary bleeding, the arrest of trickling from small veins, and the staunching of annoying hemorrhage from resected tissues. It has a wide variety of indications in surgery and general practice. Gelfoam is a unique addition to the surgical armamentarium for the control of bleeding.

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Gelfoam

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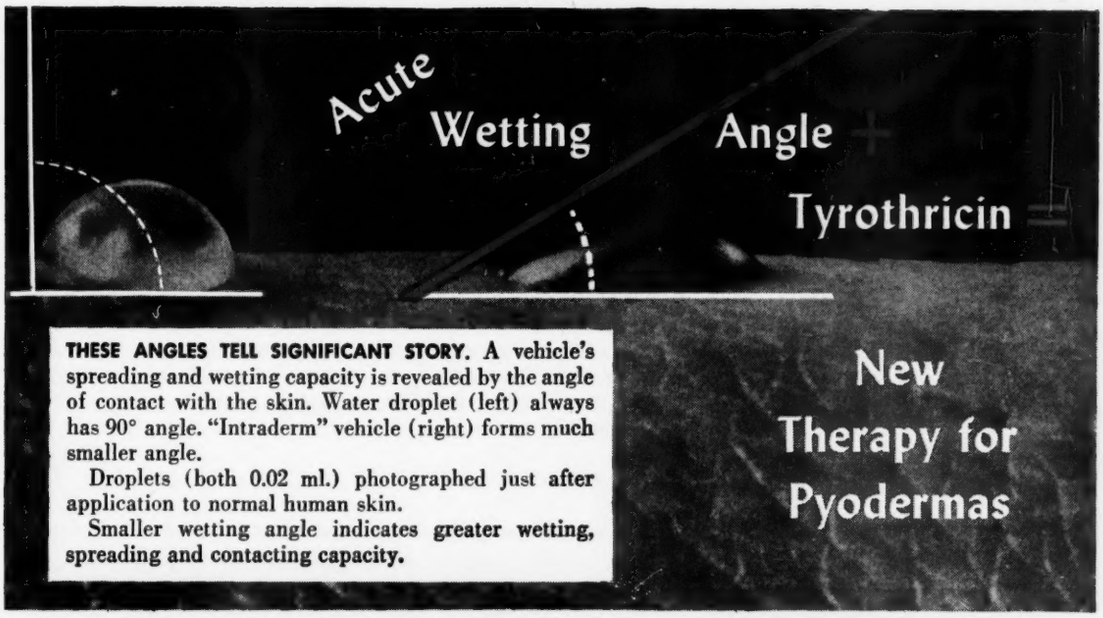
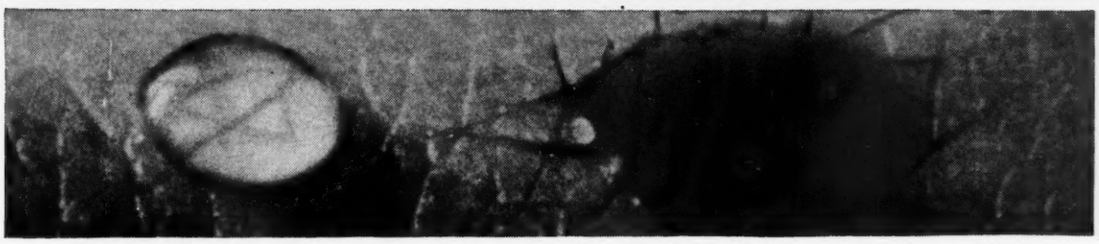
is made in sponges 20 x 60 x 7 mm. in size. Four sponges are packed in each jar.



THESE ANGLES TELL SIGNIFICANT STORY. A vehicle's spreading and wetting capacity is revealed by the angle of contact with the skin. Water droplet (left) always has 90° angle. "Intraderm" vehicle (right) forms much smaller angle.

Droplets (both 0.02 ml.) photographed just after application to normal human skin.

Smaller wetting angle indicates greater wetting, spreading and contacting capacity.



TWO MINUTES LATER. Water droplet retains shape. "Intraderm" droplet has spread and seeped into furrows. Small wetting angle demonstrates efficiency of "Intraderm" vehicle.

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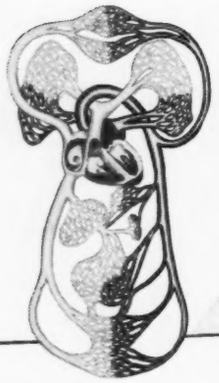

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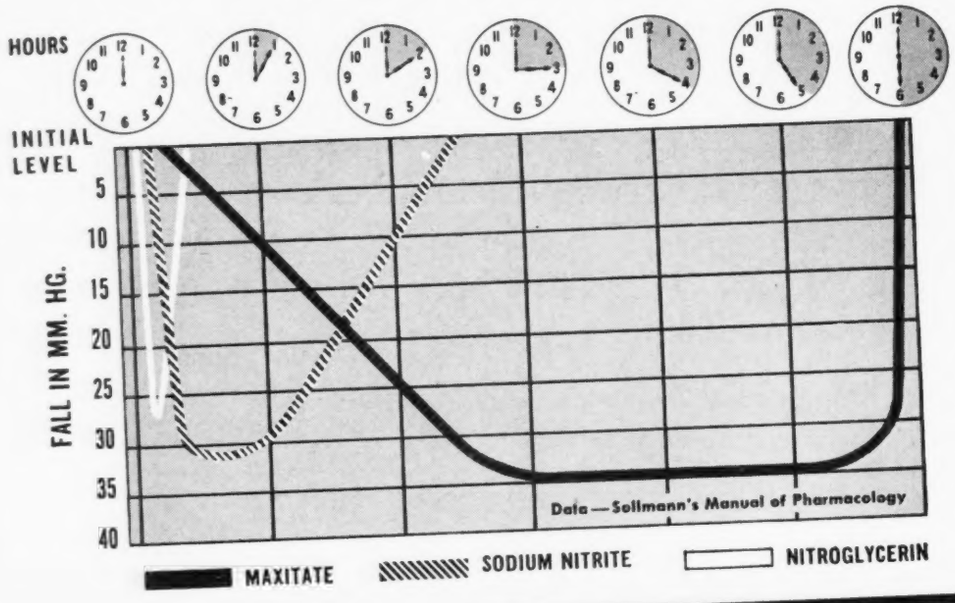

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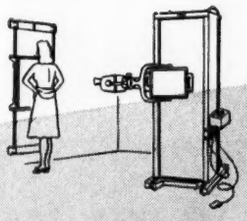

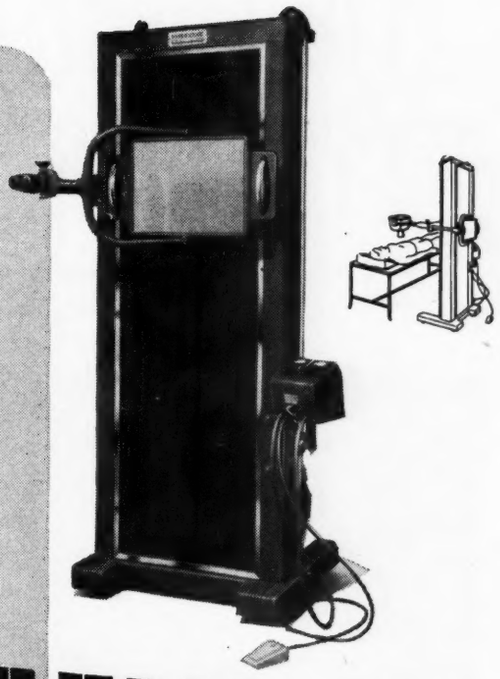

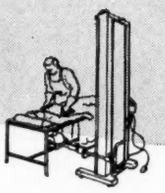

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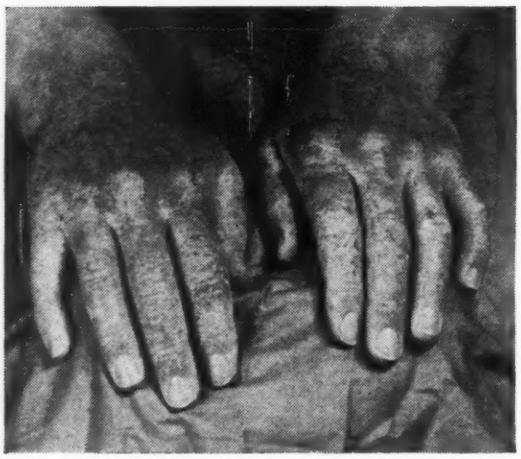
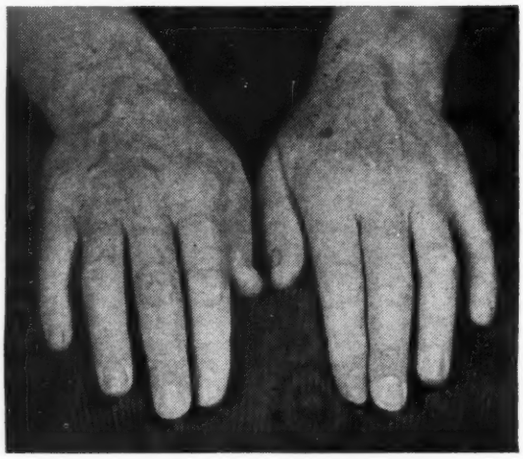
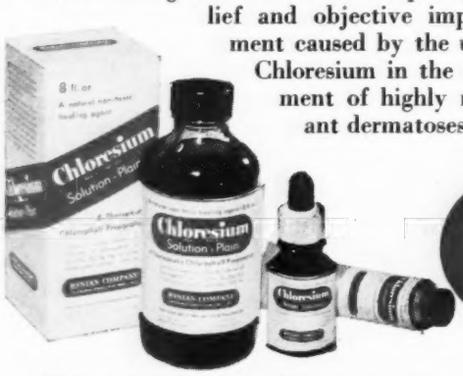




Exfoliative dermatitis of 13 months' duration. Colloid baths, cold compresses, bland oils and lotions had been tried for six weeks without encouraging results. This is one of 40 cases where a leading Clinic observed the prompt relief and objective improvement caused by the use of Chloresium in the treatment of highly resistant dermatoses.

Treated with Chloresium dressings the patient obtained almost immediate symptomatic relief and was discharged completely cleared after two weeks. There has been no recurrence. Of the forty cases which were treated with Chloresium, "all were relieved promptly of itching and burning. Thirty-six cases, or 90%, showed marked improvement objectively and thirty-two cases were completely cured. Four continue to improve under chlorophyll therapy."



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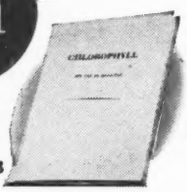

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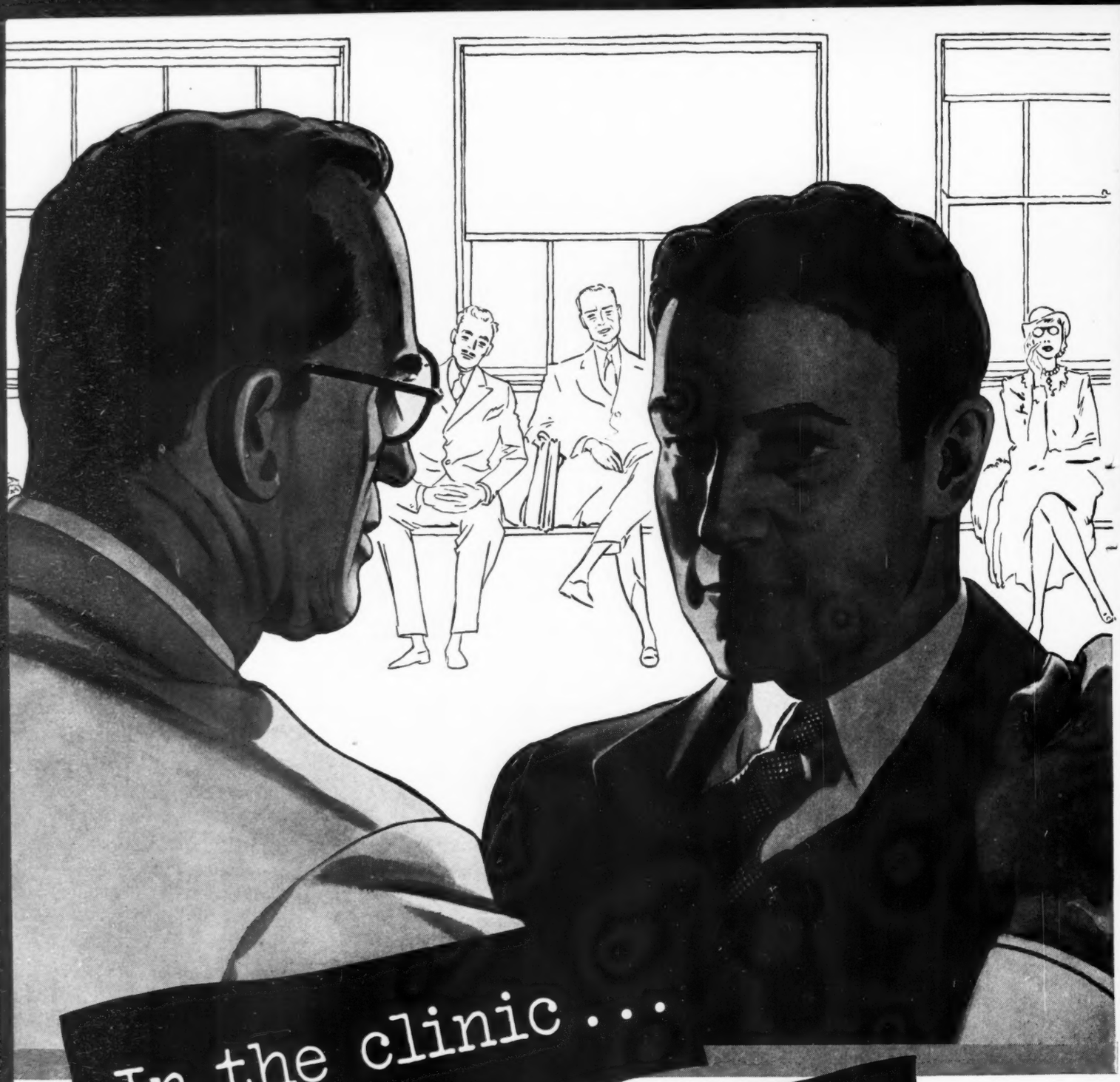

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Quantitative Aspects of Benzoyl Glucuronate Formation in Normal Individuals and in Patients with Liver Disorders*

I. SNAPPER, M.D. *and* A. SALTZMAN, M.D.

NEW YORK, NEW YORK

AFTER oral ingestion of 6 Gm. of sodium benzoate normal subjects excrete at least 4.5 Gm. of hippuric acid within four hours, that is, at least 3.0 Gm. of benzoic acid conjugated with the equivalent amount of glycine (Quick's test).[1] After ingestion of sodium benzoate not only hippuric acid but also benzoyl glucuronate appears in the urine.[2,3,4,5] Quick, in 1926, isolated this compound in pure crystalline form.[6] In previous publications, the authors with the collaboration of E. Greenspan[7,8] have shown by a qualitative method that there was a difference in glucuronic acid conjugation after the administration of equivalent doses of sodium benzoate and of benzoic acid. After 5.8 Gm. of sodium benzoate by mouth the glucuronate reactions in the urine become strongly positive. This was to be expected because Wagreich, Abrams, and Harrow[5] had shown that about 5 per cent of the ingested benzoate (5–7 Gm. dose) appeared in the urine conjugated with glucuronic acid. Their observations were in accord with the previous studies of Neuberg, and of Quick, who obtained 7 to 12 per cent and 10 to 12 per cent, respectively, in the form of benzoyl glucuronate, but gave somewhat larger doses of sodium benzoate (8–15 Gm.).[3,4] When, however, we administered 5 Gm. of benzoic acid to normal persons, the glucuronate reactions in the urine were usually negative.

We could further ascertain that the condition of the liver function has an important influence upon the excretion of glucuronates. In a series of patients with impaired liver function even the ingestion of 5 Gm. of benzoic acid resulted in the excretion of considerable amounts of glucuronates.

In this study it will be shown that the qualitative differences observed in the glucuronate excretion after ingestion of sodium benzoate and of benzoic acid can be substantiated by quantitative analyses.

The direct quantitative measurement of benzoyl glucuronate is not possible. The reducing power of the urine cannot be used for the determination of benzoyl glucuronate because it is well known that the urine normally contains reducing substances other than glucuronic acid. Quantitative methods for glucuronic acid have been devised recently, but for our purpose they cannot be used because the urine normally contains varying amounts of glucuronates.

The amount of benzoyl glucuronate can

* From the Second Medical Service of the Mount Sinai Hospital, New York.

be calculated, however, by the difference between the total benzoic acid and hippuric acid values in the urine. This method first used by J. Neuberg[3] and later by Quick[9] gives satisfactory results because after ingestion of sodium benzoate or benzoic acid no appreciable quantities of free benzoic are excreted.

In order to increase the accuracy of the determinations a few minor modifications of the method were introduced.

METHOD

Breakfast is omitted, and either 5 Gm. of benzoic acid or 5.8 Gm. of sodium benzoate are ingested within ten minutes. Lunch is allowed, but fruits and fruit juices are withheld. Powder wafers can be used to avoid the unpleasant taste, but we found it more certain and agreeable to give the dose in gelatin capsules the latter having no delaying effect on absorption. Excessive drinking of water is discouraged.

Urine is collected at two, four and six hours after the administration of the drug. The entire sample is saved. The urine is kept in the icebox until used later in the day. If left longer, it should be rendered acid to litmus.

Test for Glucuronic Acid. A one-thousandth part of the urine volume of each specimen is measured into a test tube and diluted to 2 cc. with water. If, for instance, the specimen measures 230 cc., then 0.23 cc. is taken for analysis. Two cc. of concentrated HCl and finally 2 cc. of 0.2 per cent aqueous, fresh naphthoresorcinol solution are added and mixed. The test tubes are placed in a boiling water bath for exactly ten minutes, then cooled in running water. Two cc. of amyl alcohol (*iso*) are used to extract the blue color. The color should be read immediately with a fluorescent lamp behind the tube.

Occasionally a greenish-blue or brown color appears that causes uncertainty in the reading of the test. To remove the interfering substances the lead precipitation method of Salt[10] is applied. One-thousandth of the urine volume is pipetted into each of four graduated 10 cc. centrifuge tubes, and diluted to 2 cc. with water. To the tubes respectively 0.05, 0.1, 0.15, and 0.2 cc. 5 per cent lead acetate are added, the contents mixed and centrifuged. Then one drop of lead acetate is added to each of the tubes and the tube selected in which precipitation is seen to be just complete. If no tube is completely precipitated, an additional 0.2 cc. of lead acetate is added to each and the procedure is repeated. Complete precipitation is thus effected but an appreciable excess of lead acetate is avoided. The supernatant fluid is poured from the selected tube into another centrifuge tube and N sodium hydroxide added dropwise until the first permanent precipitate of lead hydroxide is observed. Then 0.6 cc. of basic lead acetate (10 per cent) is added, the contents mixed and centrifuged. Now one drop more of the reagent is added. If this causes precipitation, an additional quantity of basic lead acetate is added. The process is repeated until a slight excess is present and precipitation is complete. The supernatant fluid is poured away and the deposit washed on the centrifuge by thoroughly stirring with 1 cc. water and separating.

The precipitate is transferred to a test tube using two 2 cc. portions of diluted HCl (1:1). Two cc. of 0.2 per cent naphthoresorcinol solution are added and mixed. The boiling and extraction of the blue color proceeds according to the method given above.

The three urine specimens are then thoroughly mixed and the volume measured. If the total volume is below 350 cc., water is added to that level. Two 20 cc. aliquots are taken for determination of total benzoic acid and similarly two 20 cc. specimens for determination of hippuric acid.

Total benzoic acid is determined by the

method of Kingsbury and Swanson[11] (using Neuberg's modification)[3] as follows:

The 20 cc. aliquots are placed into 300 cc. Kjeldahl flasks and diluted to 50 cc. Then 7.5 Gm. of sodium hydroxide, 0.5 Gm. of magnesium oxide and 2 glass beads are added, and the mixture gently boiled for one half hour on a hot plate. At the end of this time, while still at the boiling temperature, 1.0 cc. of a 7 per cent solution of potassium permanganate is added, care being taken to rinse down any permanganate that may remain in the neck of the flask with the smallest possible amount of water. The flask with its brown contents is twirled gently for a minute or two, cooled under the tap, and left at room temperature for at least two hours. Water jacketed condensers with rubber stoppers are placed on the necks, and 30 cc. concentrated nitric acid slowly poured down the side of each condenser (it is advisable to do this in a hood). The mixture is now gently boiled for forty-five minutes, cooled under the tap and the extraction with chloroform carried out.

The condenser is rinsed down with 25 cc. of water to remove any benzoic acid sublimated at the bottom of the condenser. The contents of the flask are transferred to a 500 cc. separatory funnel containing 25 Gm. of ammonium sulfate. The flask is rinsed with 20 cc. of water which is then added to the separatory funnel. After dissolving the ammonium sulfate the benzoic acid is extracted successively with one 50 cc., one 35 cc. and two 25 cc. portions of neutral, well washed chloroform. The first two portions of the chloroform are used to rinse the Kjeldahl flask. As each chloroform fraction is separated, it is poured through a folded filter paper into a second separatory funnel. The filter paper is washed with 10 cc. of chloroform.

The combined extracts in the second separatory funnel are washed once with 100 cc. of Folin-Flander's salt solution (containing 1.0 cc. of concentrated HCl in 2 liters of saturated NaCl solution). The funnel tips are dried with absorbent filter paper in order to remove remnants of the Folin-Flander's solution and the chloroform layer drawn off through a dry filter paper into a dry Erlenmeyer flask. The watery phase remaining in the separatory funnel is shaken with 20 cc. of chloroform. Again the funnel tips are dried with strips of absorbent filter paper. The chloroform is drawn off into a small beaker to which the wet folded filter paper has been transferred, thereby rinsing the paper with the chloroform. The latter is then poured through a fresh filter paper into the main bulk of chloroform in the Erlenmeyer flask.

All extractions are performed by shaking for three minutes, and allowing one half hour periods for complete separation (assisted by a few twirls). Four drops of 1 per cent phenolphthalein in absolute alcohol are added to the benzoic acid solution. Then the solution is titrated to a faint but definite pink with tenth-normal sodium ethylate (standardized against benzoic acid). Duplicates tally very closely.

Hippuric Acid (Quick's Method).[9] The aliquot of 20 cc. of urine is placed in a continuous ether extractor and acidified with 0.5 cc. of 5N sulfuric acid. The perforations of the inner extractor tube should be on a flat surface and face downwards. Ether is added, and the extractors placed in a sand bath heated by a medium sized hot plate. Water jacketed condensers are then placed in the mouths, using cork stoppers. The extraction proceeds at a rapid pace for exactly four hours, when the sand bath is removed and the extractors allowed to cool. The ether is distilled off using a water bath.

To the crystals in the 250 cc. Erlenmeyer flask, 25 cc. of concentrated HCl are added and mixed. Hydrolysis is accomplished by refluxing on the hot plate (low setting)

under an air condenser for two hours (in hood). The contents of the flask are transferred to an evaporating dish and dried completely on the water bath. The contents of the evaporating dish are then dissolved in hot water, filtered into 250 cc. beakers, washed with small quantities of water, and the filter paper washed in the dish with a further portion of hot water, filtering the latter through a fresh filter paper.

The glycine present is determined by a formol titration. The glycine containing solution obtained after hydrolysis is often colored which makes the use of indicators to determine the end points of the formol titration inadvisable. In order to avoid this difficulty we performed the titration with the help of an electrical pH indicator apparatus (Fisher titrimeter, new model). A potentiometric titration can be conveniently done with an accuracy better than 0.1 pH unit, if one uses ordinary care. The instrument is calibrated (after warm up) with a known buffer of pH 7.0 (glass and calomel electrodes, and the motor-driven glass stirrer are used). Then the glycine containing solution is neutralized to pH 7.0. Ten cc. of formaldehyde (neutralized to pH 7.0 just before use) are added, and titrated with 0.1 N NaOH to pH 8.9. Duplicates agree closely. The equivalence point of pH 8.9 was determined by formol titration of pure glycine and hydrolized hippuric acid solutions.

In order to determine the time necessary for complete extraction of hippuric acid from the urine, 300 mg. of hippuric acid were added to 20 cc. of normal urine. The hippuric acid obtained after extraction lasting for three hours, four hours and five hours was determined. With the continuous ether extractor used for these experiments, the optimal time of extraction appeared to be four hours.

COMMENTS

The results obtained are shown in Tables I, II and III. These figures indicate that the qualitative changes of the glucuronate reactions in the urine run parallel with the quantity of benzoic acid which is not conjugated with glycine.

TABLE I
ADMINISTRATION OF 5.8 GM OF SODIUM BENZOATE TO NORMAL SUBJECTS

Name	Naphthoresorcinol *	A	B	A − B	Per Cent of A
		Total Benzoic Acid, Gm.	Glycine Bound Benzoic Acid, Gm.	Non-hippuric Benzoic Acid, Gm.	
1. SA	+++ − −	4.77	4.27	0.50	(10.6)
2. SN	+++ + −	4.96	4.65	0.31	(6.3)
3. SN	+++ +++ −	5.22	4.68	0.54	(10.3)
4. GA	+++ ++ −	4.66	4.47	0.19	(4.1)
5. LI	+++ +++ −	4.91	3.76	1.15	(23.4)
6. ER	++ +++ −	5.83	5.46	0.37	(6.3)

* The plus and minus signs refer to the three 2-hour specimens collected.

After administration of 5.8 Gm. of sodium benzoate to normal persons, the glucuronate reactions in the urine are positive and the amount of benzoic acid not conjugated with glycine varies between 4.1 and 23.4 per cent. (Table I.)

After administration of 5 Gm. of benzoic acid to normal persons the glucuronate reactions in the urine are negative and the

amount of benzoic acid not conjugated with glycine varies between −3.1 and +1.2 per cent. (Table II.)

TABLE II
ADMINISTRATION OF 5 GM. OF BENZOIC ACID TO NORMAL SUBJECTS

Name	Naphthoresorcinol*	A	B	A − B	Per Cent of A
		Total Benzoic Acid, Gm.	Glycine Bound Benzoic Acid, Gm.	Non-hippuric Benzoic Acid, Gm.	
1. SA	− − −	4.85	4.79	0.06	(+1.2)
2. SN	− − −	5.52	5.57	−0.05	(−0.9)
3. GA	− − −	4.98	4.98	0.00	(0.0)
4. LI	− + −	5.15	5.14	0.01	(0.02)
5. ER	− − −	3.50	3.61	−0.11	(−3.1)
6. WA	− − −	3.82	3.85	−0.03	(−0.8)

* The plus and minus signs refer to the three 2-hour specimens collected.

After administration of 5 Gm. of benzoic acid to patients with impaired liver function the glucuronate reactions in the urine are positive and the amount of benzoic acid not conjugated with glycine varies between 5.8 and 49.8 per cent. (Table III.)

These quantitative analyses bear out the conclusion that in patients with liver impairment, the administration of 5 Gm. of benzoic acid is followed by the excretion of considerable quantities of benzoyl glucuronate. This is in contrast to findings in normal persons in whom administration of 5 Gm. of benzoic acid does not give rise to the formation of benzoyl glucuronate.

For the explanation of this difference it should be pointed out that the rate of the formation of hippuric acid is not only an index of the rapidity of glycine conjugation but at the same time of the intensity of glycine production. The liver does not store glycine but can produce it for purposes of conjugation as needed.[12] Quick has calculated that the body can produce from 0.55 to 0.7 Gm. of glycine per hour, the amount depending roughly upon the surface area of the body. Ingestion of the rapidly absorbed sodium benzoate results in a greater con-

TABLE III
ADMINISTRATION OF 5 GM. OF BENZOIC ACID TO PATIENTS WITH IMPAIRMENT OF LIVER FUNCTION

Name	Disorder	Naphthoresorcinol*	A	B	A − B	Per Cent of A
			Total Benzoic Acid, Gm.	Glycine Bound Benzoic Acid, Gm.	Non-hippuric Benzoic Acid, Gm.	
1. Cad.	Hepatitis	− − ++	1.80	1.52	0.28	(15.5)
2. Cas.	Hepatitis	− + ++	4.19	3.71†	0.48	(11.5)
3. Hir.	Hepatitis (arsenic)	+++ − −	4.26	4.00†	0.26	(6.1)
4. Can.	Hepatitis	+++ +++ ++	3.74	1.88	1.86	(49.8)
5. Stu.	Portal Cirrhosis	+++ +++ −	3.24	2.57	0.67	(20.8)
6. Mar.	Cholangiolitic Cirrhosis	+++ +++ +++	2.29	1.97	0.32	(13.9)
7. Bla.	Hyperthyroid	+ +++ ++	3.96	3.73†	0.23	(5.8)
8. Hor.	Hyperthyroid	++ +++ +	2.43	2.25	0.18	(7.4)

* The plus and minus signs refer to the three 2-hour specimens collected.
† Hippuric acid values within normal limits.

centration of benzoate in the liver than ingestion of the slowly absorbed benzoic acid.[7] In the first case the amount of glycine which the body can form is not sufficient to transform all the benzoate to hippuric acid and, therefore, part of the benzoic acid is excreted as benzoyl glucuronate. Glucuronic acid can also easily be formed in the human organism at the rate of nearly a Gm. per hour.[13] The quantities of benzoate which reach the liver during the slower absorption of benzoic acid never exceed the quantities which can be taken care of by the glycine production of the body. As a result no conjugation of benzoic acid with glucuronic acid takes place. This explanation is confirmed by slow ingestion of sodium benzoate which was proved not to give rise to formation of benzoyl glucuronate.[7]

The formation of benzoyl glucuronate after administration of 5 Gm. of benzoic acid to patients with impaired liver function can be explained in the same way. Here, the glucuronic acid evidently supplements the glycine conjugation of the benzoate which is decreased due to impairment of liver function. Quick already noted that in one patient with a liver disease who had ingested 5.8 Gm. of sodium benzoate, 21 per cent of the excreted benzoic acid was bound to glucuronic acid.[4] Several months later when her clinical condition had shown great improvement, she no longer excreted glucuronic acid when the same quantity of benzoate was again given. Quick, however, did not follow up this remarkable finding but elaborated the hippuric acid excretion after ingestion of sodium benzoate into the well known liver function test.

The compensatory conjugation of benzoic acid with glucuronic acid can be made to yield valuable clinical data; even in patients with normal hippuric acid excretion an excessive excretion of glucuronates may indicate impaired liver function. (Table III.)

SUMMARY

The amounts of total benzoic acid and benzoic acid conjugated with glycine have been determined after administration of 5 Gm. of benzoic acid to normal persons and to patients with impairment of liver function.

Under these conditions the qualitative glucuronate reactions in the urine are negative in normal persons and the amount of total benzoic acid is equal to the quantity of benzoic acid excreted in the form of hippuric acid.

Under the same conditions the qualitative glucuronate reactions in the urine are positive in patients with impaired liver function, and the amount of total benzoic acid exceeds the quantity of benzoic acid excreted in the form of hippuric acid by 5.8 to 49.8 per cent.

It follows that the ingestion of 5 Gm. of benzoic acid does not lead to the excretion of benzoyl glucuronate in normal persons. Under the same conditions patients with impairment of liver function excrete considerable quantities of benzoyl glucuronate.

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Excretion of Benzoyl Glucuronate as a Test of Liver Function*

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RECENTLY the authors have shown that the Tollens' naphthoresorcinol reaction for glucuronates may be used as a quick clinical test to reveal excessive excretion of benzoyl glucuronate.[1,2,3] In this report the clinical application of this method will be presented and several diagnostic problems will be discussed.

METHOD

Fasting normal volunteers and patients ingested 5 Gm. of benzoic acid† in gelatin capsules. Breakfast‡ was omitted. Lunch was allowed, but fruits and fruit juices were forbidden. Urine was collected at two, four and six hours after the administration of the drug. As a rule the entire sample was saved, but the loss of a *small* part of a two-hour specimen should cause no great concern, since the test is qualitative. The urine was kept in the icebox until used later in the day. If retained longer it was rendered acid to litmus.

Test for Glucuronic Acid. A one-thousandth part of the urine volume of each two-hour specimen is measured into a test tube and diluted to 2 cc. with water. If, for instance, the specimen measures 230 cc., 0.23 cc. is taken for analysis. Two cc. of concentrated HCl and finally 2 cc. of 0.2 per cent fresh aqueous naphthoresorcinol solution are added and mixed. The test tubes are placed in a boiling water bath for exactly ten minutes, then cooled in running water. Two cc. of iso-amyl alcohol are used to extract the blue color. The color should be read immediately with a fluorescent lamp behind the tube.

Occasionally a bluish-green color appears, causing uncertainty in the reading of the test. To remove the interfering substances the lead precipitation method of Salt[4] is applied.[3]

The blue color which indicates a positive reaction can be graded as one, two or three plus.

OBSERVATIONS

In normal persons neither the fasting urine nor the urine excreted after ingestion of 5 Gm. of benzoic acid shows positive naphthoresorcinol reactions with the method described. However, while it is true that the majority of normal persons have reactions which do not produce a blue color, it should be noted that the presence of a slight bluish tint in the second two-hour specimen is still within normal limits. (Table 1.) When the qualitative glucuronic acid test after the administration of 5 Gm. of benzoic acid is positive, the presence of hepatocellular damage is highly probable.

Three types of glucuronate pattern have been observed according to the time elapsing before the appearance of a positive reaction. The degree of hepatocellular damage can

† All subjects ingested benzoic acid as the acid and not as sodium benzoate; the latter causes positive glucuronate reactions even in normal persons.

‡ Glucose infusions should be discontinued while the test is being carried out.

* From the Second Medical Service, Mount Sinai Hospital, New York.

be estimated grossly from the abnormal patterns, a delay in glucuronate conjugation signifying a more severe type of liver disturbance. However, as there are exceptions to this rule, the results are usually reported as normal or abnormal glucuronate pattern. (Table I.)

TABLE I
TYPICAL GLUCURONATE PATTERNS OBTAINED AFTER INGESTION OF FIVE GM. OF BENZOIC ACID*

Normal Patterns	Positive or Abnormal Patterns		
	Minimal Damage	Moderate Damage	Severe Damage
2 hr. − −	− −	+++ +++	− −
4 hr. − +	++ +++	− ++	− +
6 hr. − −	− −	− −	+++ ++

* The qualitative glucuronate test is positive when a blue color is produced by the naphthoresorcinol method described in the text. The intensity of the blue color can be graded as one, two or three plus.

Nausea and vomiting occurred rarely, being much less frequently observed than with the routine oral hippuric acid test.

COMMENTS

Table II contains the results obtained by application of the naphthoresorcinol test to the urine after ingestion of 5 Gm. of benzoic acid. Twenty-three normal subjects and one hundred patients free from apparent hepatic disturbances showed normal glucuronate patterns without exception. In eighty-nine patients who were under study because of possible disease of the liver, the glucuronate test proved to be a useful gauge of liver function.

All of the twenty-two patients with infectious jaundice and the two patients with toxic hepatitis (arsenic) showed abnormal glucuronate patterns. This test can easily be performed on admission to the hospital, and since the results are immediately available, it assists in early diagnosis. While in the vast majority of patients with hepatitis an abnormal test was obtained on admission to the hospital, there was one exception in whom the glucuronate pattern was not immediately abnormal. When the test was repeated it yielded unequivocal evidence of severe liver damage.

TABLE II
BENZOYL GLUCURONATE EXCRETION AFTER 5 GM. BENZOIC ACID IN NORMAL SUBJECTS AND IN PATIENTS WITH AND WITHOUT HEPATIC DISORDERS

	Naphthoresorcinol Test		
	Abnormal	Normal	Totals
Normal subjects (volunteer physicians)	0	23	23
Patients having no hepatic disturbance	0	100	100
Hepatitis, catarrhal	22	0	22
Hepatitis, toxic, arsenic*	2	0	2
Cirrhosis, Laennec's	23	0	23
Cirrhosis, cholangiolitic*	1	0	1
Cirrhosis with hepatoma*	1	0	1
Thyrotoxicosis*	9	6	15
Liver metastases:			
From carcinoma of bronchus*	2	0	2
From carcinoma of gallbladder*	1	0	1
From unknown primary site*	3	1	4
From body of pancreas*	0	1	1
From sarcoma of uterus*	1	0	1
Obstructive jaundice due to:			
Stone in common duct*	0	2	2
Stricture of common duct*	0	2	2
Metastasis occluding hepatic duct[a]	0	1	1
Carcinoma of ampulla of Vater*	0	1	1
Cholangiolitis and pericholangiolitis*	0	1	1
Lymphomas[b] with liver involvement*	0	9	9

* Diagnosis confirmed by biopsy, operation, or autopsy.

[a] No metastasis to liver.

[b] Leukemia, hemoblastoma, lymphosarcoma, Hodgkin's disease, giant follicular lymphoblastoma.

Twenty-five patients with cirrhosis of the liver were studied; abnormal glucuronate patterns were found in all.

Nine out of fifteen patients with thyrotoxicosis had abnormal glucuronate patterns. In these cases it was noted that the

color was almost always intensely blue. It is probable that in the hyperthyroid patients two factors are responsible for positive results: (1) Because of more rapid absorption, more benzoic acid reaches the liver per unit time, exceeding the normal rate of glycine production and conjugation so that free benzoic acid is left to be bound with glucuronic acid. (2) Excessive glycogenolysis causes hepatic dysfunction.

The first explanation is supported by the following experience. In contrast to the results obtained in normal persons, the hippuric acid excretion after ingestion of 5 Gm. of benzoic acid by hyperthyroid patients was in several instances largest in the first two-hour specimen. However, since in hyperthyroidism other liver function tests are also frequently indicative of hepatic dysfunction, in the final analysis both factors are probably contributory.

One subject, a "normal" volunteer (not included in Table II), repeatedly showed abnormal glucuronate patterns. Nevertheless the hippuric acid excretion after 5 Gm. of benzoic acid was normal, and the cephalin flocculation of the serum was only two plus. The naphthoresorcinol test in this subject was strongly positive in the two-hour and four-hour specimens, a finding suggestive of thyroid hyperactivity. On examination a marked tremor was elicited, the thyroid gland was just palpable, and the basal metabolic rate was reported as plus 22 per cent. In this case the abnormal glucuronate pattern revealed a mild hyperthyroidism which had not been detected previously.

There exists such a galaxy of liver function tests that the introduction of a new liver function test requires justification. It is not sufficient that the determination of the glucuronate pattern after ingestion of 5 Gm. of benzoic acid is a simple procedure, or that the test described is less complicated and entails fewer errors than the quantitative determination of hippuric acid. A new reaction would be superfluous if the results merely confirmed the conclusions obtained by current liver function tests.

The following observations are reported to illustrate that although in many cases (I, II, V and VIII) the glucuronate tests run parallel with the other liver function tests, in doubtful cases (III, IV, VI and VII) the glucuronate pattern in combination with the other liver function tests may yield additional information.

CASE I. C. M., sixty-five years of age, a female, had had recurrent attacks of severe right upper quadrant pain for many years associated with intolerance to fatty food. Three weeks before admission the urine became dark, and the next day she noted jaundice which gradually increased in intensity. She lost only two pounds since the onset of jaundice. Stools were normal and there was no itching or chills.

On examination her temperature was normal; bradycardia was present. There was marked icterus of sclerae and skin. The liver was palpated two finger breadths below the costal margin and was tender, with a firm, smooth edge. The gallbladder was thought to be felt below the liver margin.

*Laboratory Data:**

Urine—bile positive	
Urobilinogen present in dil. 1:5	
Stool brown, guaiac negative	
Erythrocyte sedimentation rate 2 mm./hr.	
Hemoglobin	80%
Prothrombin index	94%, 82%, 100%, 91%
Alk. phosphatase	32, 45, 13, 22 KA units
Thymol turbidity	4 plus, 4 plus, 4 plus
Cephalin flocculation test	4 plus, 4 plus, 4 plus, 3 plus, 3 plus
Hippuric acid	2.9 Gm. in 6 hours
Cholesterol/esters	360/150 280/130
Glucuronates 2 hr.	+++ −
4 hr.	+++ +
6 hr.	+++ ++
Icterus index	27, 12, 15
Bilirubin	3.2, 3.2 mg. %

* When tests were repeated, several values are given.

Van den Bergh	prompt positive
Albumin	3.7 Gm. %
Globulin	3.3 Gm. %
Total protein	7.0 Gm. %

X-ray examination failed to demonstrate the presence of radio-opaque biliary calculi, although the outline of the caudad portion of the fundus of the gallbladder was slightly denser than the remainder of the gallbladder. Oral cholecystography showed only very faint visualization of the gallbladder.

Because of the history of biliary colic and intolerance of fat, operative intervention was contemplated on admission. However, when all liver function tests pointed to widespread liver damage this was delayed. During five weeks of observation the icterus did not subside and the sedimentation rate rose to 58 mm./hr. Finally, because of an allegedly palpable gallbladder which appeared to increase in size, exploratory laparotomy was performed. Cirrhosis of the liver was found. Biopsy showed "severe acute and chronic portal inflammation with periportal fibrosis and moderate disorganization of liver architecture. The parenchyma was rich in bile pigment. Changes appeared to be those of cholangiolitic cirrhosis."

For many years this patient had been considered to be suffering from cholelithiasis. Although in the beginning the clinical picture seemed to indicate jaundice due to common duct stones, all the liver function tests including the glucuronate pattern indicated widespread liver damage.

Case II. A. M., sixty-two years of age, a wine salesman, had lost 34 pounds in weight in the last year and a half. Although he drank much wine and other liquor, he also ate well. He had had intolerance to fatty foods for many years. Two months ago, after eating fried liver, he developed epigastric pain which lasted a few hours. At that time he also had a loose bowel movement, and his wife noted that he was yellow. The jaundice cleared after a few days.

Angiomas were found on both cheeks. The liver edge could be felt 3 cm. below the costal margin. Below the liver several observers could detect the presence of a large, firm gallbladder. A soft spleen was also just palpable.

Laboratory Data:

Urine bile	0 or 1 plus positive.
Urobilinogen	present in dil. 1:30
Stool guaiac	negative
Erythrocyte sedimentation rate	45 mm/hour
Prothrombin index	100%, 100%
Alkaline phosphatase	53 and 72 KA units
Thymol turbidity	negative
Cephalin flocc.	negative
Hippuric acid excretion	5.7 Gm. in 6 hr.
Icterus index	9
Bilirubin	1.1 mg. %
Cholesterol/esters	480/300
Galactose tolerance	0.5 Gm.
Glucuronate pattern	normal

Exploratory laparotomy revealed the presence of amorphous stones in the common bile duct. The liver was normal.

In this slightly jaundiced patient who consumed large quantities of wine the diagnosis of cirrhosis seemed obvious. However, the glucuronate pattern together with the other liver tests all indicated the presence of obstruction of the common duct. At operation this was found.

Case III. W. D., forty-seven years of age, a male, had a positive blood Wassermann in the early part of 1945 at the Red Cross Blood Bank. Although the patient was completely well and no abnormal signs could be elicited, antisyphilitic treatment was started. The first injection of neo-arsphenamine was given August 25, 1945. The second injection on September 8, 1945, was followed by severe headache, nausea, vomiting, and fever of 102.5°F. Since then he had intermittent fever, anorexia, nausea, vomiting and dark urine. On September 19th, a third intravenous injection of neo-arsphenamine was followed after a few hours by high fever, chills, headache and malaise.

On admission the temperature was normal. Sclerae were icteric. The liver was one and one-half fingers down, smooth, and non-tender. The spleen could not be felt. The urine showed 2 plus albumin, 4 plus bile; hemoglobin 70 per cent, sedimentation rate 58 mm./hr., Wassermann positive.

Table III shows the results of the liver function tests. The currently used tests seemingly indicated that the patient had an obstructive type

of jaundice. In view of the history the diagnosis of cholangiolitic type of arsphenamine jaundice, as described by Hanger and Gutman, was in order.[5] However, the glucuronate pattern after ingestion of benzoic acid indicated that even this type of arsphenamine jaundice is associated with a considerable element of liver damage.

TABLE III
COURSE OF PATIENT WITH OBSTRUCTIVE TYPE ARSPHENAMINE JAUNDICE (CASE III)

Date	Alkaline phosphatase	Icterus index	Bilirubin mg.%	Van den Bergh	Cephalin flocc.	Glucuronate pattern
9/24	11 KA units	33	3.5	prompt pos.	2 plus	abnormal*
9/29	46 KA units	42	4.5	prompt pos.	neg.	abnormal*
10/1		18	2.6	prompt pos.		
10/3	29 KA units	12	1.2	delayed		
10/9	36 KA units	12	1.2	negative	1 plus	abnormal†
10/14		7	1.0		neg.	
10/25	28 KA units					abnormal†

* The usual benzoic acid test.
† 5.8 Gm. sodium benzoate ingested in 9 portions over a 4 hour-period results in negative glucuronate reactions in normal individuals. Here the glucuronate reactions were positive.

This conclusion was helpful in the diagnosis of the following patient who actually had gallstones and in whom jaundice developed in the course of arsphenamine treatment.

CASE IV. J. H., a male, fifty-one years of age, had had two episodes of jaundice, one in 1917, the other in 1937. Six years before admission he suddenly felt severe epigastric pain which radiated to the back and up into the chest. A cholecystogram revealed the presence of gallstones.

In 1944, on the occasion of a routine checkup, signs of neurosyphilis were found, the Wassermann test being positive. He received bismuth injections at irregular intervals until February, 1946, when he was given weekly injections of neoarsphenamine. After four such injections he developed diarrhea, followed by nausea and chilly sensations. Within a week he became jaundiced, and the next day had pruritus, dark urine and clay colored stools. The jaundice remained essentially unchanged for the four weeks prior to admission, except that in the last week the stools became yellowish-brown.

On admission the temperature was normal. The pupils were irregular, did not react to light but reacted in accommodation. In the abdomen there was tenderness over the right upper quadrant. A firm liver edge was felt 3 finger breadths below the costal margin. The spleen could not be palpated.

The urine showed 4 plus bile. Urobilinogen was positive in a dilution of 1:5; erythrocyte sedimentation rate 70 mm/hr; hemoglobin 70 per cent, blood Wassermann positive.

While in the hospital the patient again experienced a severe attack of epigastric pain radiating to the back. Tenderness was elicited in the right upper quadrant of the abdomen.

TABLE IV
LABORATORY FINDINGS IN EARLY-TYPE POST-ARSPHENAMINE JAUNDICE

	Case III	Case IV
Prothrombin time (Index)	100%	100%
Alkaline phosphatase	46 KA units	35 KA units
Icterus index	42	33
Cholesterol/esters	760/245	600/300
Cephalin flocculation	2+, neg., 1+, neg.	2+, neg.
Galactose tolerance		1.9 Gm.
Thymol turbidity		1+, neg.
Hippuric acid*	5.07 Gm. in 6 hr.	5.88 Gm. in 6 hr.
Glucuronate pattern after benzoic acid 5 grams	2 hr. ++ 4 hr. +++ 6 hr. ++	2 hr. +++ 4 hr. − 6 hr. −

* 5.0 Gm. in six hours is normal.

The chemical investigations (Table IV) showed a normal prothrombin time, increase of the alkaline phosphatase of the serum, normal cephalin flocculation and thymol turbidity tests, and normal galactose tolerance. After ingestion of 5 Gm. of benzoic acid the hippuric acid excretion was normal. All these tests did not make it possible to differentiate between jaundice due to gallstones and early-type post-arsphenamine jaundice. However, the strongly positive glucuronate excretion* after ingestion of 5 Gm. of benzoic acid was sufficient to exclude common duct stone; this amount of liver damage indicated a post-arsphenamine hepatitis.

The clinicians and surgeons continued to feel uncomfortable about the diagnosis. One day they thought that a small tense gallbladder

* Quantitative determination: 5.9 per cent of excreted benzoic acid was conjugated with glucuronic acid.[3]

could be palpated, and as a consequence, exploration could not be held off any longer. The gallbladder contained stones but the common duct was completely free. Cholecystectomy was performed. Liver biopsy showed typical findings of chronic inflammation of the periportal fields and capillary bile thrombi. The diagnosis of early-type post-arsphenamine hepatitis as indicated by the glucuronate pattern had been correct. In this patient the glucuronate pattern was the only test which indicated the correct diagnosis.

Case v. P. R., a female, fifty-one years of age, had been suffering from gallstones for several years. These stones had been visualized radiographically. In addition, she also had anginal pains. There had probably been at least one episode of coronary thrombosis. During an examination in March, 1946, for new signs of coronary sclerosis, palpation of the abdomen was negative. In August, 1946, she consulted her physician because of the onset of epigastric pain and jaundice. In the two weeks prior to admission the jaundice was observed to be progressive.

On examination the liver was enlarged to one and one-half hand-breadths below the costal margin; the consistency was stony hard.

Laboratory methods showed absence of stercobilin in the stool, elevated serum bilirubin, direct Van den Bergh reaction, cephalin flocculation negative, hippuric acid excretion normal, alkaline phosphatase 28 KA units. The glucuronate pattern was normal. Therefore, the liver tests all indicated obstruction of the bile ducts with no hepatic impairment.

Exploratory laparotomy revealed carcinoma of the gallbladder with metastatic obstruction of the hepatic duct. There were metastases in the posterior abdominal wall, and in the suprapancreatic lymph nodes. The gallbladder contained numerous stones. The liver appeared free of metastasis.

In this patient the glucuronate pattern ran parallel with the other function tests. The obstructive jaundice was caused by metastases which had not as yet involved the liver parenchyma.

Case vi. R. P., a female, fifty-two years of age entered the hospital because of constant pain in the abdomen, mainly in the right upper quadrant, of eight weeks' duration. Associated with these symptoms was darkening of the urine and intermittent jaundice. Some relief was obtained by the application of hot compresses to the abdomen. Generalized pruritus and nausea were also present. She had lost 15 pounds in the past six weeks. This woman had intermittent gallbladder attacks for the past twenty years, but she never had jaundice and the liver had not been palpable.

On examination there was tenderness in the right upper quadrant with punch tenderness localized to the ninth costochondral junction. The liver was enlarged, the lower border being five finger breadths below the costal margin. The area of the gallbladder had a stony hard consistency; the spleen was also palpable.

Laboratory Data:

Urine—bile present
Urobilinogen positive in dil. 1:100
Sedimentation rate 58 mm/hr.
Prothrombin index 84%
Alk. phosphatase 28 Bodansky units
Cholesterol/esters 600/300
Cephalin flocculation negative
Hippuric acid 4.5 Gm. in 6 hr.
Glucuronate pattern abnormal 2 hr.+
4 hr.−
6 hr.−

Exploratory laparotomy was carried out and carcinoma of the gallbladder, with direct extension to liver and gastrohepatic ligament was found; a metastatic nodule was also found to obstruct the common duct. The liver, which was enlarged, contained many whitish metastatic nodules.

Although the current liver tests pointed to an extrahepatic obstructive jaundice, the abnormal glucuronate pattern indicated that in addition a general involvement of the liver parenchyma existed. This result was explained by the widespread metastases found at operation.

Case vii. D. C., a female, fifty-five years of age, was admitted a second time because of progressive weakness, fatigue, exertional dyspnea and fever. Six months previously she had entered the hospital for unexplained fever and

prostration. Examination at that time revealed hepatosplenomegaly and a slightly enlarged heart. A few small axillary lymph nodes were also found. Biopsy showed the presence of a malignant reticulum cell proliferation. Transfusions and radiotherapy were of temporary benefit.

On examination numerous, firm, matted lymph nodes were found in the axillae, cervical and inguinal regions. The liver edge was palpable 2 cm. below the right costal margin, was firm and slightly tender. The spleen filled the entire left side of the abdomen. It was firm, tender and slightly irregular.

Laboratory Data:

Urine—albumin, trace
Blood Count:
Hemoglobin 42%
R.B.C. 2,800,000
W.B.C. 4,100
Differential: Monocytosis 14%
Bilirubin 0.2 mg. %
Bromsulfalein excretion normal
Hippuric acid excretion 4.1 Gm. in 6 hr.
Glucuronate pattern negative

Despite many transfusions and radiotherapy the course was gradually downhill, with terminal development of ascites and pleural effusion. Postmortem examination revealed hemoblastosis* involving lymph nodes, liver and spleen.

We have obtained negative glucuronate patterns in patients with lymphomas† having liver involvement. This may prove useful in deciding against the diagnosis of hepatic cirrhosis.

Case VIII. B. P., a female, forty-nine years of age, had a thyroidectomy for thyrotoxicosis sixteen years before admission. She was well until eight years before admission when intractable itching and patches of xanthelasma appeared on the eyelids. Jaundice was noted six years before the present admission, at which time cholelithiasis was diagnosed. At operation gallstones were found, and a cholecystectomy performed. After the operation the jaundice persisted and the generalized pruritus became worse. While most of the stools were brown, on several occasions they were clay colored. Six weeks ago patient began to have diarrhea six to ten times daily, which persisted.

The skin was icteric and excoriated. An enlarged liver, rather tender, could be palpated with its border at the level of the umbilicus. The spleen was not enlarged.

Laboratory Data:

Urine—bile 4 plus
Urobilinogen positive in dil. 1:40
Stercobilin was present in the stool
Erythrocyte sedimentation rate 94 mm/hr.
Hemoglobin 88%
Galactose tolerance normal
Hippuric acid 2.6 Gm. in 6 hr.
Icterus index 30
Alk. phosphatase 25 KA units
Cephalin flocculation 1 plus
Prothrombin index 88%
Total protein 6.7 Gm. %
Cholesterol/esters 360/280
Glucuronate pattern normal

The jaundice was believed to be due to chronic obstruction of the common bile duct, caused either by stone or by a scar forming after the first operation. This diagnosis seemed justified in view of the almost normal cephalin flocculation test and the cholesterol ester ratio. On the other hand the alkaline phosphatase of the serum was not as much increased as expected in a case of obstructive jaundice of long standing, and the hippuric acid excretion was low. The glucuronate excretion being negative excluded generalized liver damage.

At operation the surgeons were convinced that cirrhosis of the liver was present. A tremendously enlarged liver, with a slightly nodular surface, and a greatly dilated hepatic artery and portal vein were found. The common bile duct could not be dissected as it was buried beneath dense adhesions. Liver biopsy, however, showed that the preoperative diagnosis had been correct. The specimen "consisted of a fragment of liver showing evidence

* Hemoblastosis is defined as a morbid process affecting the hematopoietic system with features of invasive growth as well as hyperplasia of spleen and liver, as in leukemia, but without any abnormality of the blood picture.

† See Table II.

of chronic bile stasis (considerable number of bile thrombi, and bile pigment in Kupffer cells) and lymphocytic cells in periportal areas; general picture as found in obstructive icterus. Since normal architecture of liver lobules was not altered, cirrhosis can be ruled out."

From this case it may be concluded that although the glucuronate pattern is a relatively sensitive indicator of liver damage, it still remained negative in a patient with obstructive jaundice of very long standing.

SUMMARY

1. A simple liver function test is described which is based on the presence of excessive excretion of benzoyl glucuronate in the urine after ingestion of 5 Gm. of benzoic acid. The test is non-toxic and can be performed quickly. In selected cases, when used in conjunction with the current liver tests, it has important diagnostic application.

2. The test was studied in twenty-three normal volunteers, in a control series of 100 patients who had no obvious hepatic disturbances, and in eighty-nine other patients in whom hepatic disturbances were suspected.

3. In all normal volunteers, and in patients without hepatic disturbances the test was negative.

4. In all cases of hepatitis and portal cirrhosis the test was positive.

5. The test was also positive in some patients with thyrotoxicosis and in most cases of hepatic metastasis. It was negative in all of nine lymphomas.

6. Application to two cases of early-type post-arsphenamine jaundice is described. In both cases hepatocellular damage was indicated by positive tests. In one the diagnosis of arsphenamine hepatitis was made in the presence of gallstones.

7. The glucuronate reactions remained negative in a patient with obstructive jaundice of very long standing.

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A Note on Studies of Hemolysis in Paroxysmal (Cold) Hemoglobinuria*

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THIS is a brief preliminary note on studies relative to the mechanism of hemolysis in paroxysmal (cold) hemoglobinuria. The observations were made while studying a syphilitic negro male complaining of abdominal pain and dark urine after exposure to cold. The Donath-Landsteiner reaction[1] as done by a routine technic[2] was positive. Since there have been repeated clinical and experimental observations suggesting that some factor or factors other than cold may play an important rôle in the hemolytic mechanism of the disease,[3,4,5] the following work was done. The experiments are divided into three groups: (1) The first confirms Hijmans van den Bergh's observation[4] that CO_2, under specified *in vitro* conditions, may effect the hemolysis of this disease; (2) the second indicates carbonic anhydrase inhibitors may, under certain circumstances, prevent the hemolysis; (3) the third shows that definite morphological changes of the erythrocytes occur prior to hemolysis.

PROCEDURES

Group O erythrocytes were washed four times and resuspended in normal saline in 5 per cent concentration. Fresh guinea pig serum diluted 1:5 with normal saline was employed as complement. Serum was obtained from blood drawn from the patient and from normal subjects into warmed syringes and tubes. These components were proportioned as shown in Charts 1 and 2. All tests were run in duplicate. The quantitative technics employed for CO_2, cyanide and sulfanilamide determinations have been described elsewhere.[6,7,8] Hydrogen ion determinations were made with a Beckman meter at 27°C. The meter was calibrated repeatedly with a standard reference solution.

Experiment No. 1. CO_2, helium and oxygen were collected in rubber bags and bubbled through pipettes into the combinations under oil for five minutes, as shown in Chart 1. The gases were collected in rubber bags and allowed to stand at the desired temperature before using, in order to avoid the cooling effects of a rapidly expanding gas. Additional controls were also set up under oil but did not receive any gas. As shown in Chart 1, hemolysis occurred only with CO_2 at 27°C. The pH of such a combination was 6.4 (8 volumes per cent CO_2) and that of the combinations receiving oxygen or helium was 7.5 to 7.6. However, other observations suggest that the effect of CO_2 may not be due simply to a lowering of the pH, as it seems to be in nocturnal hemoglobinuria.[9] The pH of identical combinations was lowered to 6.2 by using saline acidified with HCl. Hemolysis did not occur. Nor did bubbling nitrogen into such acidified combinations under oil cause hemolysis, thus suggesting the CO_2 effect may not have been the summated result of lowered pH and trauma. Furthermore, a routine Ham test[9] was negative. The entire

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CHART I

TEST TUBE	PT. SERUM (CC)	CONT. SERUM (CC)	COMPL (CC)	NORM. SALINE (CC)	CONT. R.B.C. (CC)	C O_2	H_E	O_2	HEMOLYSIS AT 27°C	HEMOLYSIS AT 37°C
1	0.5		0.2	0.1	0.2	5 MINS			++++	0
2		0.5	0.2	0.1	0.2	5 MINS			0	0
3	0.5		0.2	0.1	0.2		5 MINS		0	0
4		0.5	0.2	0.1	0.2		5 MINS		0	0
5	0.5		0.2	0.1	0.2			5 MINS	0	0
6		0.5	0.2	0.1	0.2			5 MINS	0	0

CHART 1. Shows the degrees of hemolysis following the addition of carbon dioxide, helium or oxygen to various combinations at 27°C. and 37°C. Complete hemolysis is indicated by ++++.

procedure was repeated at 37°C. after all the materials had stood at 37°C, for an hour. (Chart 1.) CO_2 did not cause hemolysis at that temperature. The serum hemolysin was then adsorbed on erythrocytes at 2°C. No hemolysis resulted from bubbling CO_2 at 25°C. into combinations similar to those of Chart 1 but made with serum from which the hemolysin had been adsorbed. Combinations containing the hemolysin and as low as 2.6 volumes per cent of CO_2 hemolyzed readily on chilling and warming.

Experiment No. 2. Cyanide and sulfanilamide inhibit the activity of carbonic anhydrase but sulfathizaole and sulfadiazine do not.[10] After several preliminary experiments the sodium salts of sulfanilamide, sulfadiazine, sulfathiazole and cyanide were employed in 0.008, 0.006, and 0.005 M. concentrations as shown in Chart 2. The pH of such combinations were 7.6 to 7.5 (27°C.). These tubes were chilled at 2°C. for ten minutes, then incubated at 37°C. for two hours. Hemolysis at the end of that time was absent or present only in traces in the presence of cyanide and sulfanilamide; but hemolysis in those tubes containing equal amounts of sulfathiazole and sulfadiazine was practically complete. That cyanide and sulfanilamide did not destroy the hemolysin was demonstrated by the following experiment. Sulfanilamide and cyanide were added to two aliquots of serum in even higher concentrations (0.1 M.). The solutions were allowed to stand for three hours and then dialysed through cellophane bags suspended in normal saline for twenty-four hours. At the end of that time there was no detectable sulfanilamide and no more than a trace of cyanide in the sera. Both samples of serum retained their hemolytic activity as shown by Donath-Landsteiner tests, indicating the persistence of an active hemolysin. That these salts did not destroy the serum complement was shown by the hemolytic effect of such dialysed serum on sensitized sheep erythrocytes. The inhibition of hemolysis by sulfanilamide and cyanide, therefore, did not

CHART 2

TEST TUBE		PT. SERUM (CC)	COMPL. (CC)	CONT. R.B.C. (CC)	SODIUM CYANIDE (CC)	SODIUM SULFANILAMIDE (CC)	SODIUM SULFATHIAZOLE (CC)	SODIUM SULFADIAZINE (CC)	pH .008 M.	pH .006 M.	pH .005 M.	HEMOLYSIS .008 M.	HEMOLYSIS .006 M.	HEMOLYSIS .005 M.
CHILL AT 2°C AND WARM AT 37°C	1	0.5	0.2	0.2	0.1				7.6			0		
	2	0.5	0.2	0.2	0.1					7.5			0	
	3	0.5	0.2	0.2	0.1						7.5			TRACE
	4	0.5	0.2	0.2		0.1			7.6			0		
	5	0.5	0.2	0.2		0.1				7.6			SL. TRACE	
	6	0.5	0.2	0.2		0.1					7.6			TRACE
	7	0.5	0.2	0.2			0.1		7.6			+++		
	8	0.5	0.2	0.2			0.1			7.5			+++	
	9	0.5	0.2	0.2			0.1				7.5			+++
	10	0.5	0.2	0.2				0.1	7.6			+++		
	11	0.5	0.2	0.2				0.1		7.6			+++	
	12	0.5	0.2	0.2				0.1			7.5			+++

CHART 2. Shows the degrees of hemolysis of various combinations following chilling for ten minutes at 2°C. and incubating for two hours at 37°C. Complete or almost complete hemolysis is indicated by +++.

result from destruction of the hemolysin or complement. It was a reversible inhibition.

Experiment No. 3. Suspensions of washed Group O erythrocytes in the patients' and controls' sera were studied microscopically. To the control sera was added enough lecithin to produce spherocytosis but not hemolysis. As has been shown, spherocytosis so produced causes no demonstrable alteration in cell volume.[11] First such suspensions were chilled to 2°C. for ten minutes, then placed in chilled hemocytometers and studied microscopically. Several hundred measurements of diameters of the cells in the control sera were made with a calibrated ocular-micrometer. No measurements were made on control suspensions after they had stood in the hemocytometer for more than four minutes in order to avoid evaporation with increased tonicity of the solutions. From such values the mean corpuscular volume (MCV) was calculated and checked by routine hematocrit and red blood cell counting methods.[2] Similar ocular-micrometer measurements were then made on the same control erythrocytes chilled in the patient's serum and the MCV recalculated. While at very low temperatures the erythrocytes suspended in the patient's serum showed no or only occasional spherocytosis. Biconcave cells were prominent. However, as the hemocytometer warmed to room temperature the cells assumed a spherical appearance and gradually faded from view. Calculations ($V = 4\pi r^3/3$) made from measurements of diameters of these spherocytes indicated no marked increase in cell volume. However, within a few seconds prior to the leakage and escape of hemoglobin the diameter of many of the lysing cells increased appreciably. Whether this was a result of an actual terminal increase in volume or simply a result of collapse of stroma associated with a loss of hemoglobin remains to be studied.

CASE REPORT

W. B. (J. H. H. history number 359265) was a 33 year old negro male who entered Johns Hopkins Hospital on December 5, 1945, with the complaints of abdominal pain and passage of dark urine following exposure to cold. The family history was non-contributory. The past

history revealed the patient had always enjoyed general good health until the present illness. In 1930, the patient had a penile sore and was given "needle treatment" by another clinic.

The present illness was dated by the patient as beginning three years prior to admission. He noticed short periodic attacks of nausea, cramping abdominal pain and vomiting associated with the passage of dark urine. These attacks occurred from a few minutes to several hours following chilling and exposure to cold. Between such episodes the patient was asymptomatic. During the summer months the attacks did not occur. The patient stated the abdominal pain would last only an hour or so and then disappear. This would be followed soon by the passage of dark urine. The urine would clear in a few hours and the patient would remain asymptomatic until subsequent exposure to cold. Exercise did not seem to precipitate an attack. The last episode of such symptoms had occurred a few days prior to admission following prolonged exposure to chilling of the feet during a hunting trip.

The physical examination revealed a temperature of 98.6°F.; pulse 64; respiration 20; and blood pressure 166/85. The patient was a well developed, well nourished colored male in no discomfort. The skin was moist. There were no eruptions. The pupils were round, regular and equal and reacted to light and accommodation. The retinae showed no lesions. The extra-ocular movements were well performed. The external auditory canals were clear. Hearing was intact. The nasal septum was in the midline and not perforated. The nares were clear. The mucous membranes were of good color. The tongue protruded in the midline without tremor. There was no papillary atrophy. There was no pharyngeal or tonsillar injection. The neck was supple. The trachea was in the midline and the thyroid was not enlarged. There was no unusual cervical pulsation. Precordial dullness was not increased extending only to the mid-clavicular line in the left fifth interspace. There were no shocks, thrills or any unusual precordial activity. Heart sounds were of good quality. There was a soft systolic murmur at the apex that was not transmitted. Abdominal examination revealed no masses or tenderness. No abdominal organs were palpable. The genitalia showed no scars. Neurological examination revealed no abnormalities.

Laboratory Data: The serological tests for syphilis were positive. Erythrocyte count was 4.31 million per cubic milliliter, hemoglobin was 11.8 Gm. per cent. Hematocrit was 35.7 per cent. The mean corpuscular volume was 83 cubic microns and the mean corpuscular hemoglobin concentration 32 per cent. Leukocyte count was 8,300. The sedimentation rate corrected to 1. The differential count showed 67 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 13 per cent lymphocytes, 19 per cent monocytes. The Ehrlich and Donath-Landsteiner tests were positive. Urine was dark with a specific gravity of 1.005, alkaline reaction and contained 2 plus albumin. There were no reducing substances. Microscopic examination showed 5 to 10 leukocytes per high power field but no casts or erthrocytes. Non-protein nitrogen was 123 mg. per cent. Phenolsulphonphthalein excretion was 38 per cent at the end of two hours. Serum bilirubin was 0.8 mg. per cent. The total serum protein was 7.06 Gm. per cent with albumin 4.19 and globulin; 2.87 urea clearance showed 48 per cent at the normal maximum. Cerebrospinal fluid showed a positive serological test for syphilis, 17 mg. per cent of protein, a negative mastic curve and 8 lymphocytes per cubic milliliter.

Stool examination was negative; *X*-rays of the chest and abdomen were interpreted as showing no abnormalities. On December 11, 1946, the non-protein nitrogen was 55 mg. per cent. *Diagnosis:* Syphilis, late, latent. Paroxysmal (cold) hemoglobinuria associated with impairment of renal function. In a period of thirteen days the patient was given 4,000,000 units of penicillin intramuscularly. He is now being followed in the Johns Hopkins Hospital Dispensary.

CONCLUSION

Under certain specified circumstances the addition of CO_2 to the serum from a patient with paroxysmal (cold) hemoglobinuria causes hemolysis. This effect of CO_2

depends on the presence of a serum hemolysin. Evidence suggests it may not be due simply to a lowering of pH and occurs at temperatures which alone do not cause hemolysis. Sulfanilamide and cyanide, two substances which inhibit the activity of carbonic anhydrase, block the effect of this hemolysin in concentrations that do not destroy either the hemolysin or the complement. Their inhibitory effect is reversible. Preceding hemolysis the erythrocytes undergo marked morphological changes.

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Review

Bacillus Pyocyaneus Infections*

A Review, Report of Cases and Discussion of Newer Therapy Including Streptomycin (Concluded)

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INTRACRANIAL INFECTIONS

A. Pyocyaneus Meningitis. Meningitis may occur as an extension from a neighboring focus in the sinuses or mastoids and as a localized infection of the meninges without systemic involvement especially following introduction of the organism during lumbar puncture or through cranial-cerebral trauma. It is a much more frequent complication of pyocyaneus sepsis than is endocarditis. The first proved case of meningitis due to this organism was reported in 1893 by Kossel.[59] Florence Evans[58] reviewed the literature on this subject in 1936, at which time she was able to find a total of forty cases (including two cases of Ehlers,[57] neither proved, and two cases ascribed to Charrin,[56] but which were those of Ehlers); eighteen of these were primary meningitis without generalized infection. She added three new cases of primary meningitis, all of which followed lumbar puncture. Since this time a number of other cases have been described.[88–101]

The report of Botterell and Magner[101] (1945) merits special consideration. Eleven cases of meningitis associated with penetrating head injuries were seen in patients evacuated from France during the Normandy campaign. They were all severe injuries. Nine patients died; two recovered. There were four cases of brain abscess; it seemed likely that B. pyocyaneus was present in three of these cases on admission. On admission in one other case the organism was cultured from the temporal muscle which was in communication with the subarachnoid space. In four cases the source seemed to be cross-infection (three from leaving a tube in the wound for repeated instillation of penicillin). Bacteriologic check showed that B. pyocyaneus was air-borne in some of the wards, all of which were crowded. In two cases it was thought that the meningeal infection resulted from intrathecal injection of contaminated penicillin. Although bacteriological check showed that the dispensed penicillin was sterile, the dregs of some of the bottles contained B. pyocyaneus. Infections with gram-positive organisms were well controlled with penicillin.

In Chart A the forty-one cases of primary B. pyocyaneus meningitis reported to this time are summarized. Thirty-two (78 per cent) of the total were the direct result of lumbar puncture and/or the introduction of contaminated solutions into the spinal or cranial subarachnoid space. Treatment has consisted in repeated spinal drainages and, recently, the use of sulfonamide compounds parenterally, orally

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CHART A

SUMMARY OF CASES OF PRIMARY B. PYOCYANEUS MENINGITIS REPORTED IN THE LITERATURE

Author	No. of Cases	Origin	Outcome
Schlagenhaufer[67] (1911)	5	Infections followed spinal anesthesia (contaminated saline solution)	3 died 2 recovered
Chauffard and Laroche[70] (1917)	1 Age 20	Intraspinal administration of contaminated tetanus antitoxin	Recovery
Abadie and Laroche[71] (1918)	1	Craniocerebral trauma (laceration of dura by shell fragments)	Recovery
Sonnenschein[75] (1923)	1 Age 20	Lumbar puncture	Death in 11 days
Schneider[77] (1924)	1 Age 17	Spinal anesthesia	Recovery in 3 months; (B. pyocyaneus in blood *after* onset of meningitis)
Levy and Cohen[79] (1925)	1 Age 32	Lumbar puncture	Sterile spinal fluid in 1 month Recovery
Valls, Palazzo and Ottolenghi[81] (1928)	1	Gunshot wound in lower spine	Recovery in 1 month Received autogenous vaccine treatment
Vaughan, Beck and Shelton[85] (1931)	1 Age 40	? Focus in nose with direct extension or bacteremia; possibly from lumbar puncture ?	Recovery in 2 months
Ghon[86] (1932) (observed in 1905)	1 Infant	Infected spina bifida	Death
Shrewsbury[87] (1934)	1 Age 34	Spinal anesthesia	Recovery in 6 weeks
Bhatnagar[88] (1934)	1 Age 40 Male	Spinal anesthesia	Death in 7 days
Evans[58] (1936)	3	Lumbar puncture	Recovery in 1 case Death in 2 cases
Ibrahim[91] (1937)	1	Lumbar puncture	Recovery
Berger[93] (1938)	1	Lumbar puncture	Recovery
Iwasake and Motinaga[98] (1939)	1	Pneumoencephalography	Not known
Wise and Musser[94] (1939)	6	Lumbar puncture (contaminated Hg manometer)	2 deaths 4 recoveries
Kerman, Perlstein and Levinson[99] (1943)	1	Pneumoencephalography	Death
Botterell and Magner[101] (1945)	11	Penetrating head wounds (during Normandy campaign). Six from contaminated penicillin	9 deaths 2 recoveries
Evans, F. T.[100] (1945)	2	Spinal anesthesia	Death in both

(and intrathecally).[94] With the addition of these compounds it would seem that the prognosis is somewhat improved. The mortality rate was 55 per cent (of forty). Of those thirty-two cases resulting from lumbar puncture, spinal anesthesia, etc. twelve died, a mortality rate of 39 per cent (of thirty-one—outcome not known in one).

As seen on Chart B there have been twenty-eight cases reported in which the diagnosis of *Bacillus pyocyaneus meningitis secondary to a focus elsewhere* seemed reasonably certain. To this we add one case (Case H. B.). There were six instances of infection of newborn infants, presumably through the umbilicus. Two of the adult cases had an associated endocarditis.[50,55] As would be expected where there was usually a primary disease, in itself grave, and where the meningitis was simply a terminal or additional complication, the prognosis is much worse. The mortality in this group was at

CHART B

SUMMARY OF CASES REPORTED IN THE LITERATURE OF B. PYOCYANEUS MENINGITIS SECONDARY TO A FOCUS ELSEWHERE

Author	Age	Primary Condition	Outcome	Other Findings
Kossel[59] (1893)	6 weeks	Otitis media	Death	At autopsy, B. pyocyaneus isolated in pure culture from meninges and heart blood and in combination with pneumococci from middle ear and lung
Pesina and Honl[60] (1894)	Adult		Death	B. pyocyaneus and Friedländer's bacillus isolated from purulent meningeal exudate
Councilman, Mallory and Wright[61] (1898)		No information		
Perkins[19] (1901)	25	Abortion followed by sepsis	Death	B. pyocyaneus isolated from uterus with Staphylococcus aureus. B. pyocyaneus isolated in pure cultures from liver and meninges. Fibrinopurulent endometritis also present
Berka[62] (1903)	52	Pneumonia (?)	Death	
Horder[63] (1904)		Chronic otitis media	Death	Pure cultures. B. pyocyaneus from both middle ears, lungs and meninges
Rolly[55] (1906)	28	Abortion followed by sepsis	Death	Acute endocarditis of mitral valve due to B. pyocyaneus (old rheumatic mitral stenosis)
Hubener[64] (1907)	18	Pelvic abscess	Death	Renal abscess
Benfey[65] (1907)	8 days	Infection of umbilicus	Death	
Lagniffoul, Bousquet and Roger[66] (1910).		Sepsis resembling typhoid fever	Death	
Fraenkel[68] (1912)	23	Sepsis without obvious focus	Death	No symptoms of meningitis. B. pyocyaneus cultured from brain at autopsy
Gaethgens[69] (1914)		Tuberculous meningitis	Death	B. pyocyaneus cultured from brain at autopsy. B. pyocyaneus may have been introduced by lumbar puncture
Fraenkel[3] (1917)	1	Chronic otitis media	Death	Infection of pharyngeal mucous membrane and cecum
Canelli[72] (1919)	2½ months	Enteritis; sepsis	Death	Sibling also died with B. pyocyaneus sepsis a few days before
Dudden[73] (1922)	3½	Sepsis, possibly from focus in middle ear	Death	
Neal[76] (1924)	7	No details given	?	
Kliew and Koch[78] (1924)	4	Stomatitis	Recovery	
Chiari[80] (1926) 3 cases	Under 10 days	Probably infection of umbilicus	Death in all three	All had purulent pericarditis. B. pyocyaneus observed in intestinal contents of one infant (? portal of entry)
Gaucheraud and Pigeaud[82] (1928).	Newborn	Infection of umbilicus	Death in 37 days	Mother at birth had septic endometritis with infected amniotic fluid
Leadingham[83] (1930)	20	No obvious B. pyocyaneus infection	Death	B. pyocyaneus from heart blood at autopsy. 3 month pregnancy. Diagnosed as "toxic encephalitis." *Culture from brain and meninges sterile.* No histological evidence of meningitis

CHART B.—(*Continued*)

Author	Age	Primary Condition	Outcome	Other Findings
Baumeister[84] (1931)	24	Sepsis without obvious focus	Recovery after prolonged illness	Hemorrhagic lesions on the mucous membranes of the mouth, and on the skin
Bezi[37] (1933)	2	Otitis, mastoiditis, lat. sinus thrombosis, sepsis	Death	Ecthyma gangrenosum. Gastrointestinal and pulmonary lesions
Neih[90] (1936)	13	Mastoiditis with extension to the meninges	Death	
Roberts and Belsey[92] (1937)	31	Secondary infection of tuberculous empyema cavity with bacillus pyocyaneus (with bacteremia presumably)	Recovery	
Slutsky and Matlin[95] (1939)	49	Sepsis with the focus in the right kidney	Death	
Allin[96] (1941)	Newborn	Infection of umbilicus	Death in 6 days	Intracranial hemorrhage. Congenital atalectasis of the left lung
Kraus and Hunter[97] (1941)	Newborn	Probably infection through umbilicus. Mother had enteric infection with chills and fever and diarrhea with B. pyocyaneus in stools while in labor	Death in 20 hours	Generalized macular rash at birth
Moragues and Anderson[50] (1943).	66	Infection of genitourinary tract	Death	Diabetes mellitus. Acute B. pyocyaneus endocarditis of mitral valve

least 86 per cent. The treatment has generally been unavailing, though recently sulfonamides and streptomycin have been used. When employed in the treatment of meningitis, streptomycin should be given intrathecally as well as systemically in large doses.

B. pyocyaneus has also been implicated as the cause of rhinitis and hemorrhagic meningitis in pigs.[104a]

B. Brain Abscess. There are only three reports concerning brain abscess due to B. pyocyaneus in addition to that of Botterell and Magner.[101]

1. Galavotti[102] described a two and one-half-year-old child who had convulsions every one or two months for eighteen months, with right hemiparesis and evidence of pronounced increase in intracranial pressure. At autopsy three communicating abscesses each 3 to 4 cm. in diameter were found in the left hemisphere, as well as suppuration of both choroidal plexuses. The pathogenesis in this case was not clear although the wall of one of the abscesses was subjacent to a forceps scar. There was no history of sepsis and no fever.

2. Bocchini[103] described a two and one-half-month-old infant with bilateral abscesses of the anterior part of the choroid plexuses with extension into the adjacent walls of the ventricles. There was a short period of fever at the age of fifteen days; following this the main symptoms were those due to the rapidly increasing hydrocephalus.

3. The report of Cianci[104] was primarily concerned with the bacteriology of a cerebral abscess, and no details are given other than that B. pyocyaneus was recovered in pure culture and that there was a preceding acute otitis media.

ARTHRITIS AND OSTEOMYELITIS

Cases of arthritis and osteomyelitis due to the B. pyocyaneus have been so rarely reported that brief summaries of the eight known cases (and one highly doubtful one) are appended. Two other cases[47,143] have been mentioned about which there are no details available. In seven instances it seemed highly probable that the involvement was metastatic, but Schein's case[110] was the only one in which positive blood culture proved this supposition.

Perkins[19] described a case of a thirty-year-old man who had pneumonia and evidence of fluid in the left pleural cavity. Later an abscess about the left seventh rib and acute purulent arthritis of the left elbow developed, Thick, greenish foul-smelling pus from which B. pyocyaneus was isolated was drained from both of these locations. On resection of the rib in the abscess floor there was no apparent connection between the abscess cavity and the pleural cavity. The patient died a short time later; there was no autopsy.

Waite's case[3] was that of a twenty-year-old female who had sudden onset of chills and high fever followed by intense pain and much swelling of one knee joint. Ten days after the onset a portion of the head of the tibia was resected. In the joint was a large amount of pus from which B. pyocyaneus was isolated in pure culture. Part of the tibia and the patella were necrotic. After two weeks in a cast a mid-thigh amputation was performed because of progressive infection of bones and soft parts. The patient improved rapidly and was discharged in two weeks. There was no mention of the origin of the infection.

Grove's case[105] was that of an eight-year-old boy who contracted secondary infection with B. pyocyaneus after operation for tuberculosis of the left hip joint. During a septic course of approximately two months' duration he developed purulent arthritis of the right thumb and of the right hip joint. He was treated with autogenous vaccine to which the author attributes his rapid recovery. Although B. pyocyaneus was obtained only from the original site of infection (the other sites were not cultured), it is quite likely that the other suppurative foci were metastatic.

Pinelli[106] described a case of an eight-month-old baby who had fever of unknown etiology for six days at the age of six months. During the month before admission the child had been pale and sickly and had fever ranging from 38° to 39°c. and night sweats. The baby cried every time her shoulder was touched and avoided moving the left arm which was immobile and semi-flexed. Aspiration of the red and fluctuant shoulder joint produced 6 cc. of turbid, thin, odorless, slightly greenish pus from which B. pyocyaneus in pure culture was isolated. A few days later aspiration was repeated and vaccine therapy by intramuscular injection was begun. Only one other aspiration was necessary and recovery was rapid with normal function of joint restored.

Melina[107] described a case in a ten-year-old girl whose illness began with pain in the right hip and fever as high as 40°c. Later chills, intermittent fever, sweats and dry cough were persistent. Twenty days after onset a right thoracentesis produced 70 cc. of yellow-green serous fluid which was not cultured. One month after onset signs of the right pleural effusion persisted. Atrophy of the right hip was present and there was pain over the greater trochanter and sciatic region. *X*-ray revealed much destruction of the head of the right femur with involvement of the ischium and detachment of the head of the femur from the acetabulum. Aspiration of the hip produced slightly purulent serosanguineous fluid from which the B. pyocyaneus was isolated in pure culture. Her condition remained stationary

despite vaccine therapy and was unchanged when her parents took her home six weeks after onset of the illness.

Bishop[108] described a case of osteomyelitis and arthritis in a three and one-half-year-old boy. B. pyocyaneus infection in an area of first and second degree burn of the right leg and foot was followed by multiple subcutaneous abscesses and pyarthrosis of the right ankle joint with *x*-ray evidence of beginning destruction of the lower tibial epiphysis. After incision and drainage, he recovered rapidly. Fifteen months later he was re-admitted with recurrent inflammation of the right ankle joint associated with fever and night sweats. On incision and drainage of the joint, B. pyocyaneus was found in the pus. Autogenous vaccine was given. By the thirtieth day after admission the wound was well healed.

Bormioli[109] described an unusual case of acute osteomyelitis of the sternal manubrium which was considered to be the result of metastasis from a large furuncle on the right arm. (No cultures reported from the boil.) Following removal of the sequestrium which consisted of nearly the whole manubrium recovery was rapid. B. pyocyaneus was isolated in pure culture from the area of osteomyelitis.

Schein[110] reported a case of a fifty-six-year-old man who was cystoscoped because of bilateral renal lithiasis. This procedure was followed by chills and fever, prostration and delirium. From the urine a pure culture of B. pyocyaneus was grown. Blood culture was sterile. He was given a total of 27 Gm. of sulfanilamide for a period of nine days with improvement of symptoms and subsidence of fever. Soon after discontinuing the medication the patient noted pain and tenderness over the lower dorsal segments of the spine and the return of fever, 102 to 103°F. daily. The urine continued to yield B. pyocyaneus on culture. Blood culture revealed B. pyocyaneus on the thirtieth hospital day. Sulfanilamide was again given; this time for six days, a total of 34 Gm. Temperature subsided and remained normal. Seven weeks after onset of sepsis *x*-ray evidence of osteomyelitis of the seventh and eighth dorsal vertebrae was obtained. There were also suggestive findings of a soft tissue abscess in the adjacent mediastinum. Further treatment consisted in the application of a plaster jacket. Convalescence was prolonged (about one year), but was uneventful. A year later culture of the urine still showed B. pyocyaneus.

The case reported by Fiset[111] was that of a seventy-two-year-old farmer who had suffered from progressive "chronic articular rheumatism" for ten years. He had anorexia and alternating constipation and diarrhea. There was slight periarticular edema, muscular atrophy in the limbs, and a "light deforming hypertrophy of the small articulations, mainly fingers." There was a low grade fever, 99° to 100°F. B. pyocyaneus was cultured in "striking abundance" from the stools. The patient's serum agglutinated the organism in dilutions of 1–600 (fifty-one controls had no higher titer than 1–20). It was considered that he suffered from intestinal infection with B. pyocyaneus, and that the arthritis was "a part of the picture." He was treated with vaccine by mouth for three months, at the end of which time the agglutination titer was 1–1100. After fifteen days he was asymptomatic. He had no relapses for three years.

From this report the causal relationship of the B. pyocyaneus to the arthritis is not clear. There was no suppuration of the joints, and it was not proved that there were any intestinal lesions. It is not clear why a vaccine given by mouth should have any effect on an infection of the gastrointestinal tract.

Other reports of osteomyelitis include one case with vertebral involvement[47] and one case (location not stated) inadequately

treated with streptomycin reported by Herrell and Nichols.[143] No details are given in either of these reports.

INFECTIONS OF THE EYE: CORNEAL ULCER

Involvement of the eye with B. pyocyaneus usually takes the form of a corneal ulcer, although the cases of necrosis of the eyelids,[2,31] dacrocystitis,[112] conjunctivitis[113] and punctate keratitis[114] are notable exceptions. Despite its rarity, it forms an important entity because the usual course without treatment, or with only local measures, is that of progressive extension of infection into the other parts of the eye, leading to loss of the globe.[115] B. pyocyaneus is said to be the most virulent organism that attacks the cornea; infection leads to panophthalmitis[124,133] even more certainly than with the streptococcus, staphylococcus or pneumococcus. When ulceration occurs, it almost invariable follows trauma to the cornea due to the presence of a foreign body or its removal; the organisms are not infrequently introduced through the use of contaminated solutions of fluorescein[120] or boric acid[132] instilled after such manipulations. B. pyocyaneus will live in 4 per cent boric acid.[132]

The first recognized case of corneal ulcer was reported by Sattler[116] (1891). Compilation of reported cases in the review papers by Mauersberg,[117] Jacobi,[118] Morelli[119] and Joy[115] totaled sixty-four cases in 1942. Since that time, sixteen more have been added, making a total of eighty cases. This latter group is tabulated in some detail in the accompanying table (Chart C) because of the good results which have been brought about by the use of the sulfonamide drugs, particularly sulfapyridine, sulfadiazine and sulfanilamide. This is in contrast to older methods of treatment.

Treatment. The traditional vigorous local therapy consisting of hot packs, atropinization, irrigation and instillation of various antiseptics, incision of the cornea and actual cautery of the ulcerated area, was almost uniformly unsuccessful in preventing loss of the eye. Experimentally, twenty-four to thirty-two hours after inoculation of the cornea of the rabbit, the presence of bacilli in normal corneal tissue often far removed from the site of inoculation could be demonstrated.[125,126,127] Presumably this was brought about by lymphatic spread and affords a ready explanation for the inefficacy of local treatment which has so often been observed clinically.

The demonstration, also in rabbits, that the sulfonamides penetrated into the tissues of the eye in significant amounts[128] has pointed the way to a rational form of treatment. Sulfapyridine and sulfanilamide attain higher concentrations in the aqueous and the cornea than sulfadiazine and sulfathazole.[129,130] For this reason, Joy[115] used sulfapyridine in the therapy of experimental infections with excellent results, although his dosages were so high as to make them inapplicable to man. This work, however, has had ample confirmation clinically.[120,124,131]

von Sallman showed[121] that much higher levels of the sulfonamides could be obtained in the anterior segments of the eye by iontophoresis than with other methods. Sodium sulfadiazine entered in larger amounts than any of the other sulfonamides, and this method was superior to other means of administration of this drug and to other local treatment. However, the best results were obtained by a combination of iontophoresis, local application of sulfadiazine powder and oral administration of sulfadiazine. He treated two patients each with a large corneal ulcer, iritis and high hypopyon with this combined therapy with good final results in both.

Although nothing further has been published by von Sallman on this subject the iontophoretic method, particularly when combined with other sulfadiazine therapy,

CHART C

SUMMARY OF CASES OF CORNEAL ULCER DUE TO B. PYOCYANEUS WHICH HAVE BEEN REPORTED SINCE TREATMENT WITH THE SULFONAMIDES HAS BEEN USED

Year	Author	No. of Cases	Initial Injury to Cornea	Treatment	Outcome	Remarks
1941	Lepard[120]	3	Unstated types of foreign body (industrial workers)	Local treatment	Enucleation	
				Local plus sulfanilamide late in the course of disease	Enucleation	Total corneal involvement
				Local plus sulfapyridine	Thin scar at site of ulcer. Vision 20/20 25 days after injury	B. pyocyaneus cultured from fluorescein solution used in eye
1941	Rudolph (discussion under Lepard)	2	Not stated	Sulfathiazole by mouth. 5% sulfathiazole locally. "Delimiting keratotomy" 10th day. Sulfacetamide 4 Gm. late in course of disease	Evisceration	Panophthalmitis
				Glacial acetic acid applied to ulcer. Sulfacetamide 4 Gm. late in course of disease. Corneal paracentesis 8th day	Evisceration	Ulcer spread over entire cornea
1941	Cooper (discussion under Lepard)	4	Unstated types of foreign body (industrial workers)	Sulfathiazole 2 days, sulfapyridine after 2nd day	Progress of infection checked	Secondary glaucoma developed. Eye later enucleated.
				Sulfathiazole 1 day, sulfapyridine after 1st day. Local cautery 14th day	Ulcer healed slowly. Iridectomy 2 months later. Final vision 20/60 with correction	Apparently healing ulcer spread widely after cautery
				Sulfathiazole 1 day, sulfapyridine after 1st day	Enucleation	Slow progression to panophthalmitis
				Sulfathiazole 1 dose, sulfapyridine after 1st dose	Large corneal scar without useful vision	
1942	von Sallman[121]	2	Not stated	Oral administration of sulfadiazine, sodium sulfadiazine solution by iontophoresis into anterior eye, and local application of sulfadiazine powder	"Good final results" in both	Both ulcers large with hypopyon and iritis
1942	Solomon[122]	1	Sand spur	Local treatment with stropine, zinc sulfate, hot applications, etc. Foreign protein injections ("Lactogen"). On 40th day, neoprontosil	Thin scar over pupil. Some useful vision remained	Rapid improvement after neoprontosil begun
1943	Goldberg[123]	1	Not stated	Sulfathiazole, 4 Gm. daily by mouth	Cured. Vision 20/20 bilaterally	Multiple superficial ulcerations bilaterally. Treatment begun early, before results of cultures known
1943	Brown[124]	3	Not stated	Sulfadiazine by mouth	Enucleation	Progressive infection
				Sulfathiazole by mouth	Enucleation	Progressive infection
				Sulfapyridine by mouth (All had local treatment)	Large corneal scar. Vision 10/400	Healed completely in two months

would seem to be the method of choice. When facilities for this type of treatment are not available, either sulfapyridine or sulfanilamide by mouth or parenterally is the drug of choice. Nothing has been published concerning the effect of streptomycin on this type of pyocyaneus infection, but it is quite likely that this agent will also be effective in treatment of corneal ulcers.

INFECTIONS OF THE EAR

A. Otitis Externa. (See also section on skin infections). In the tropics, especially during the rainy season, inflammation of the auricle occurs rather commonly.[134] There is pain, often excruciating, a seropurulent discharge from the ear with partial or complete occlusion of the meatus, low-grade fever and regional lymphadenitis. The process may spread peripherally to involve the skin over the mastoid and face.[135] Only rarely does the inflammation proceed to "boil" formation. The pronounced increase in incidence during the wet season, at which time "prickly heat" is also quite common, causes the use of the term "hot-weather ear." This accents the strongest etiological factor; the constantly moist, macerated skin in areas of contact is especially susceptible to infection.

The B. pyocyaneus, either in pure culture or associated with Corynebacterium ceruminis is found in the discharge in many cases.[134] Other instances are due to fungi.

In many patients the infection is difficult to cure and recurrences are frequent. The most important consideration is to keep the ear dry; as a corollary to this, it is necessary to avoid ear plugs or other devices worn while bathing which promote maceration of the epithelium. Local therapy has consisted of heat, boric acid lotion, boroiodine powder and phenyl mercuric nitrate 1:1250 in 95 per cent alcohol.[136] Vaccine has also been used with some good results. It would be expected that the sulfonamides and streptomycin would be as efficacious here as elsewhere.

B. Otitis Media. In the usual instance in which B. pyocyaneus is cultured from a draining ear, the process is a chronic one and the organism obviously a secondary invader.[31] An occasional example of apparently primary otitis media has also been reported.[59] The presence of bacilli in large numbers in the pharyngeal exudate in these cases affords a logical explanation as to the pathogenesis. Mastoiditis and thrombophlebitis of the lateral sinus with septicemia[37,90] are uncommon complications. Six of the reported cases of meningitis[2,37,59,63,73,90] were preceded by otitis media; direct extension could not be demonstrated in some cases in which bacteremia was present[37,90] so it is likely that these instances were due to blood-borne metastases.

RESPIRATORY TRACT

Infection of the respiratory tree is relatively unimportant in pyocyaneus infection because it is infrequently involved primarily and is rarely the portal of entry for the organism.

Kossel[59] (1894) described two fatal cases in children in both of whom there was otitis media, in one associated with purulent pansinusitis, and in the other with purulent rhinitis, laryngitis, tracheitis and enteritis.

Ulceration of the pharynx, tonsils and buccal mucosa with formation of an extensive necrotic membrane simulating that in scarlet fever or diphtheria has already been described as part of the lesions of the gastrointestinal tract. Smaller ulcerations involving the larynx, trachea and bronchi have been discovered at autopsy by Fraenkel,[2] Bezi[37] and Rolly.[55] In one instance these occurred in a patient with pulmonary tuberculosis who also had tuberculous ulcers of the larynx and bronchi, but the two were easily differentiated by the characteristic finding in the former of masses

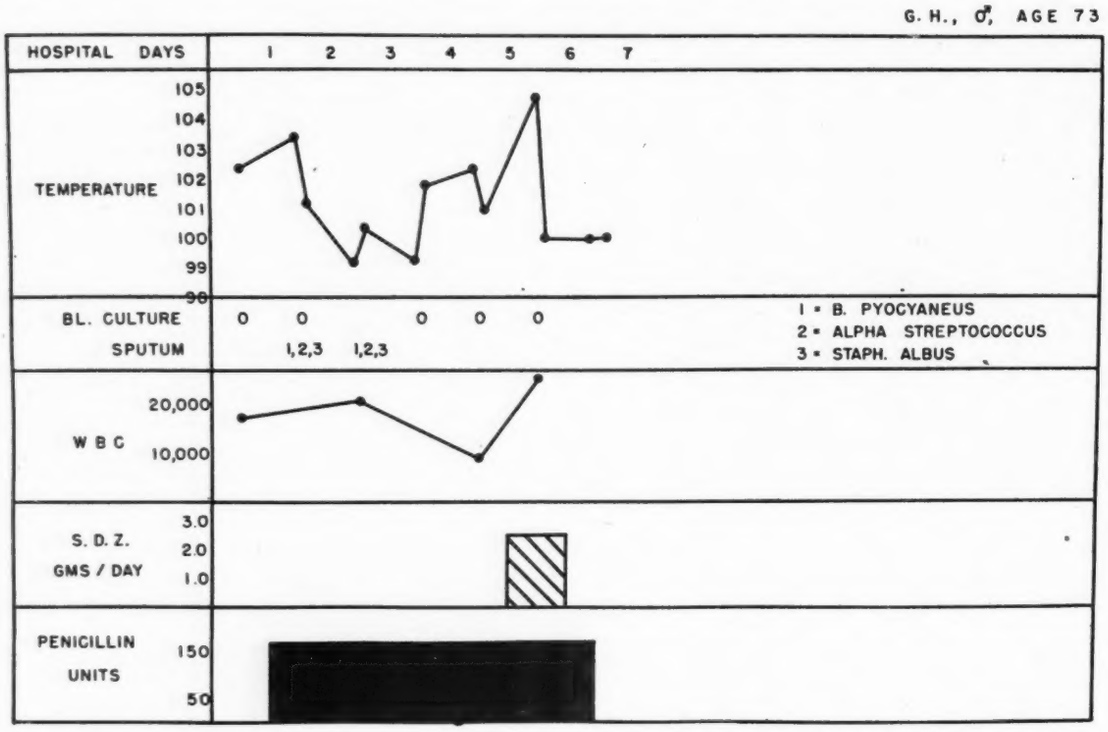

FIG. 7. Case x. Rapidly fatal course with treatment of pyocyaneus pneumonia and empyema with penicillin and sulfadiazine.

of gram-negative slender bacilli in the blood vessel walls and by the presence of B. pyocyaneus in the blood terminally.

Primary invasion of the lung, with pneumonitis as the principal illness, has been rarely seen. Fraenkel's case[2] of a twenty-year-old soldier whose lung abscess drained spontaneously into a bronchus and was followed by long-continued expectoration of thin, fetid, purulent sputum containing B. pyocyaneus in large numbers is an example. The clinical diagnosis in this instance was not confirmed as there was no surgery performed. Our Case x is another rare instance of primary pneumonitis.

In the cases described as bronchopneumonia,[34,37] inadequate histological detail prevents judgment as to whether or not the processes were metastatic or ectogenous. The former type of lesion is the only one recorded in the reports which contain detailed microscopic accounts.[2,17,26] Thus in many cases of sepsis (Case 1), the lung exhibits multiple 5 to 10 mm. areas of necrosis with peripheral hemorrhage in the centers of which the involved arterioles can be seen. Throughout the necrotic areas and in the walls of the blood vessels, large masses of slender gram-negative rods can be characteristically demonstrated.

The case described below was apparently primary pneumonitis (Case x), a very unusual condition. The relation of the aspirated lipoid material to the terminal illness is not clear because it was obvious that the pneumonitis caused by this material was quite old. It is probable that it resulted from the use of oily nose drops in the treatment of sinusitis.

CASE x. This patient had bilateral pneumonia due to B. pyocyaneus followed by empyema. (Fig. 7.) Penicillin and sulfadiazine therapy was employed and his course was rapidly downhill.

G. H. was a seventy-three-year-old, white male account collector who was admitted com-

plaining of cough and left pleuritic chest pain. Acute frontal sinusitis sixteen years prior to admission was followed one year later by a radical operation on the left frontal sinus. Since this time he had had recurrent episodes of purulent nasal and postnasal discharge and occasional spontaneous epistaxes. There had also been a chronic, non-productive cough for several years.

Acute rheumatoid arthritis, involving the hands, elbows, knees and feet occurred ten years prior to admission. During the five years prior to admission, the process had been quiescent, but some difficulty in walking had persisted due to the deformity.

Four days prior to admission a nosebleed occurred. A few hours later a cough began which became productive of yellow sputum. Pain on coughing or deep breathing was noted over the left anterior chest twenty-four hours later; oral temperature was 101.4°F. The following morning, two days prior to admission, he was afebrile and felt improved. During these next two days, however, the fever returned, the cough became worse and the sputum assumed a rusty tinge. There were no chills or chilly sensations.

Physical examination revealed the temperature to be 103.8°F., pulse 135, respiration 34, blood pressure 100/65. The patient was a well developed, elderly man, acutely ill but not in great distress. The pharynx was diffusely reddened and there was a purulent postnasal discharge. Respirations were moderately rapid and shallow. There was a lag in respiratory excursion on the left. There was increased tactile and vocal fremitus, dullness to percussion and bronchovesicular breath sounds over the left base, posteriorly. Coarse, moist inspiratory râles were heard over all lung fields, more prominently on the right. Heart and abdomen were normal. There were deformities of the hands and feet characteristic of chronic rheumatoid arthritis in a quiescent stage.

Laboratory examination showed the following: Blood Hinton was negative. Urine was normal on admission and subsequently also, except for slight microscopic pyuria and hematuria while there was an inlying catheter in the bladder. Hemoglobin was 11 Gm. per cent on admission; two days later, after a 500 cc. transfusion, hemoglobin was 15 Gm. per cent and hematocrit 46.5 per cent. Total white blood count was 17,600 per c. mm. on admission, 20,200 per c. mm. on the second hospital day, fell to 9,000 on the fourth day, but rose again to 25,150 on the fifth day (day before death). Blood non-protein nitrogen was 57 mg. per cent on admission.

Although there were gram-positive cocci seen in the stained smear of the sputum on admission, culture revealed that the predominant organism was B. pyocyaneus on both the first and second hospital days. Sputum contained also small numbers of alpha streptococci and Staphylococcus albus. Blood cultures on the first, second, fourth and fifth days were sterile.

Electrocardiogram taken on the third day showed a sinus arrhythmia, rate 120 per minute, low voltage and slurring Q-R-S complexes, and inversion of T_2 and T_3, normal axis. Five hours later there was uncontrolled auricular fibrillation with a ventricular rate of around 180 per minute.

Chest *x*-ray on admission revealed diffuse density throughout the left lung field, with a localized area of homogeneous density at the base of the upper lobe and a similar linear area at the base of the lower lobe. There was mottled density throughout the right lung field. There was an increase in the transverse diameter of the heart. A bedside *x*-ray on the fourth day showed insignificant resolution of the bilateral pneumonic process.

Penicillin, 20,000 units every three hours intramuscularly, was begun on admission and continued until death. Oxygen by B.L.B. mask was started later on the first day. A 500 cc. whole blood transfusion was given also during the first day. There was a large amount of thick, tenacious, mucopurulent sputum produced, which required frequent suctioning to prevent obstruction of the trachea. On the second day, a pleural friction rub was heard at the base of the right axilla. Despite these findings, he appeared to improve slowly during the first three days in the hospital. The temperature gradually fell to normal, and regression of the signs of consolidation on the left occurred, though there then appeared signs of dullness and bronchial breathing at the right base, and the friction rub persisted in this location. During the third day he developed

auricular fibrillation with a rapid ventricular rate, which was not slowed markedly by administration of 1.6 mg. of lanatoside C. Later that day, he suddenly became cyanotic and cold, and there was extreme dullness with absent breath sounds over most of the right lung, posteriorly, with deviation of the trachea to the right. These phenomena were almost completely reversed in a short time after a catheter had been introduced into the trachea and large amounts of secretions aspirated. His temperature slowly rose and during the fourth day stayed around 102°F. rectally. At bronchoscopy it was demonstrated that the bronchi to the right lung were almost completely occluded by secretions, and marked improvement in respiratory exchange seemed to follow their removal by this method. However, physical signs of absolute flatness below the seventh rib laterally on the left, with a friction rub in this location as well as on the right were noted. During the early part of the fifth day, the temperature was 104 to 105°F. rectally. He was given 2.5 Gm. of sodium sulfadiazine intravenously, and 3,000 cc. fluids intravenously. During the next twelve hours there was a steady fall in temperature to normal. On the morning of the sixth day, after appearing much improved, he suddenly became cyanotic and died in a short time, apparently of obstruction of his airway.

GROSS PATHOLOGY. *Pleural Cavities:* The left pleural cavity contained 1,000 cc. of thin, turbid, blood-tinged fluid. The left lower lobe appeared collapsed and atelectatic. There were dense fibrous adhesions binding the base of the left lung to the parietal pleura and the dome of the diaphragm. On breaking through these adhesions, a large amount of purulent fibrin-filled fluid was evacuated. The surface of the pleura was ragged and yellow with a considerable amount of inflammatory exudate, which was contained in the walled-off pockets.

The right pleural cavity was largely obliterated by numerous fibrous adhesions and contained about 50 cc. of yellow, turbid fluid. There were numerous adhesions, between the pleura and the pericardium. The pleural surface was grayish-pink and somewhat ragged where the adhesions were torn.

Lungs: The right lung weighed 920 Gm. About 3 cm. above the base of the lung, the surface was puckered and fissured as if drawn in by a tight constriction. This area was hard in consistency and somewhat nodular. There was rather firm consolidation of the entire right lower lobe, and the lower 2 cm. of the right upper lobe. The right middle lobe was less densely consolidated, but was definitely firmer than normal. The pleural surfaces were smooth, moist and dark grayish-pink in color. There were many fine adhesions between the visceral and parietal pleura, particularly between the pleura and the pericardium. On cutting through the right lower lobe in the constricted area, there were numerous nodular areas, grayish and grayish-white in appearance, in some places having the gross characteristics of caseation necrosis. These areas were moderately well circumscribed but were numerous and occupied the main portion of the lower third of the right lower lobe. The remainder of the right lower lobe and the right middle and the lower portion of the right upper lobe showed moderately dense consolidation. Only the apex of the right upper lobe showed the normal crepitation and aerated appearance. The bronchi were patent and contained no exudate. The bronchial and hilar lymph nodes were normal in size and moderately anthracotic.

The left lung weighed 560 Gm. The base of the left lung was very adherent to the dome of the diaphragm with numerous fibrous adhesions. There were fibrinous and easily torn fibrous adhesions along the entire surface of the left lower lobe, which was rubbery in consistency. Aside from the adhesions, and the area of inflammatory exudate around the bone, the pleura was smooth, moist and grayish-pink in color. The left upper lobe showed some crepitation and aeration. However, the left lower lobe was completely atelectatic. On cut surface the left lower lobe was dense, dark red in color and rubbery in consistency. The left upper lobe was moderately well aerated and grayish-pink in color. The bronchi were patent and showed no exudate. The arteries and veins showed no antemortem thrombi or emboli in either lung.

Spleen: The spleen weighed 220 Gm., was firm and moderately engorged. On the surface there were several small, slightly pale, depressed areas which had the appearance of infarcts.

Liver: The liver weighed 1,440 Gm., was very firm and the yellowish-brown color on cut surface was distinctly pathological. Over the anterior surface of the right lobe there was an area of fibrous thickening in the region of the attachment of adhesions to the diaphragm.

MICROSCOPIC PATHOLOGY. *Lungs:* The firm scarred area in the right lower lobe showed diffuse, chronic infiltration with fibrosis and foreign body giant cell reaction to fat. The normal pulmonary architecture in this area was completely obliterated. In the center of this region there was a cyst-like cavity filled with amorphous eosinophilic granular matter and round or oval vacuoles representing fat. This lesion was consistent with reaction to aspirated lipoid material. In the remainder of the lobe there was pronounced diffuse acute purulent bronchitis and bronchopneumonia with the alveolar spaces and bronchioles filled with polymorphonuclear leukocytes and macrophages. In the exudate there were slender bacilli. There were many large fat vacuoles scattered through the areas of acute inflammation and contained in many of the macrophages. In the left lower lobe there was marked generalized congestion and partial atelectasis. There was only a small amount of purulent exudate in the bronchioles and alveoli, and much less acute inflammation than in the right lower lobe. Small numbers of bacilli and bacilli and cocci were seen in the exudate.

Liver: There was extensive central degeneration and necrosis of the liver cells with slight infiltration with polymorphonuclear leukocytes and macrophages. In one section frequently marked congestion and hemorrhage were associated with the focal lesions. No significant vascular lesions were found. No bacteria were present. In a broad zone beneath the capsule there was marked fibrosis extending into and replacing the parenchyma to a considerable degree. In this zone of fibrosis, proliferation of bile ducts and infiltration with chronic inflammatory cells were present.

Spleen: There was diffuse congestion and infiltration with polymorphonuclear leukocytes. There were numerous large, irregular areas of necrosis which were more densely infiltrated with acute inflammatory cells; some of these lesions were undoubtedly infarcts.

There was pronounced atheromatosis of the aorta. Generalized renal congestion was present.

Bacteriology: Right lower lobe of lung: B. pyocyaneus, B. mucosus, non-hemolytic staphylococcus aureus, and B. coli. *Left lower lobe of lung and left main bronchus:* B. pyocyaneus, nonhemolytic staphylococcus aureus, and B. mucosus.

Final Pathological Diagnosis: Diffuse bilateral bronchopneumonia and acute bronchitis (see bacteriology); bilateral empyema (pleural); atelectasis of the left lower lobe of the lung; lipoid pneumonia, healed, right lower lobe of lung; central necroses of liver, marked, and acute splenitis and multiple infarcts of spleen.

TREATMENT

There is a wide variation in the spontaneous course of systemic infections depending upon many factors, such as presence of other serious disease, virulence of the organism, route of introduction of the organism, the location of foci and their accessibility to surgical drainage, presence of intravascular foci such as endocarditis, and lateral sinus thrombophlebitis. In general, however, when there is repeated or prolonged bacteremia, the outcome is fatal in untreated cases.

Vaccines. The principal agent used in treatment of all types of B. pyocyaneus infections until nine years ago was autogenous vaccine. Assay of the results is difficult, although in several[35,105] instances it apparently influenced favorably what seemed to be a generally downhill course. There are many more examples of failure of such treatment.[2] Since the introduction of the sulfonamides and streptomycin, it has seldom been used.

Sulfonamides. Since the report of Soeters[137] in 1937, describing the recovery from sepsis in a child treated with prontosil, the various sulfonamides have been extensively employed for all types of infections. The results have often not been dramatic, although these drugs undoubtedly repre-

sented a great improvement over other forms of therapy previously known, both in effectiveness and in ease of administration. The variation of *in vitro* sensitivity of strains of B. pyocyaneus isolated from untreated patients is considerable;[115] some strains are relatively resistant. Sulfadiazine is the sulfonamide of choice because of the low rate of toxic reactions, although the other members of the group are effective also. Under certain conditions in the treatment of corneal ulcer, sulfanilimide or sulfapyridine may be preferable because of their greater ability to penetrate into the tissues of the eye (see section on eye infections).

One should not lose sight of the few simple precautions necessary for protection of the patient during sulfonamide therapy. These include the maintenance of an adequate fluid intake so that the urinary output is at least 1,500 cc. daily, frequent estimation of blood sulfonamide levels and hemograms, and careful observation for other evidences of toxicity such as fever, rash or jaundice.

Streptomycin. Since the initial description of streptomycin by Schatz, Bugie and Waksman[140] in 1944 there have been few reports of its use in treatment of B. pyocyaneus infections in experimental animals[141] and in man.[142,143] The total of such cases treated in this institution is still small so that one can only gain some preliminary impression as to its effectiveness. Of the three patients with sepsis reported herein treated with streptomycin none survived. The presence of associated disease was a factor which influenced the outcome in each case. Again, there is great variation from strain to strain in sensitivity of the organism to streptomycin. Thus, in Case II (H. B.) whose organism was sensitive to 10 units per cc. the blood stream was sterilized without difficulty, while in Case III (C. L.) there was no effect on a bacteremia caused by an organism resistant to 500 units per cc. Both these patients died, although there can be little doubt that under more favorable circumstances the treatment would have been curative in the former instance.

In the treatment of meningitis streptomycin should be administered intrathecally, 100,000 units daily, as well as intramuscularly. The therapy in Case II (H. B.), in whom meningitis certainly contributed to the fatal outcome, conceivably would have been completely successful if he had received the drug in adequate dosage directly into the spinal fluid.

CHART D

CHANGES IN SENSITIVITY TO STREPTOMYCIN OF THE VARIOUS ORGANISMS CULTURED FROM PATIENTS DESCRIBED IN THIS REPORT

Case	Before Treatment	Following Treatment
II	B. pyocyaneus inhibited by 10 units/cc.	(Blood sterilized)
III	B. pyocyaneus resistant to 8 units/cc. (inhibited by 16 units/cc.)	Resistant to 500 units/cc.
IV	B. pyocyaneus inhibited by 12 units/cc.	Resistant to 50 units/cc.
	B. coli inhibited by 4 units/cc.	Resistant to 200 units/cc.
VI	B. coli inhibited by 8 units/cc.	B. coli resistant to 200 units/cc.
	B. proteus inhibited by 8 units/cc.	
	B. pyocyaneus inhibited by 12 units/cc.	
	B. mucosus inhibited by 12 units/cc.	
VII	B. coli inhibited by 8 units/cc.	B. coli resistant to 200 units/cc.
	B. pyocyaneus inhibited by 12 units/cc.	
	B. mucosus inhibited by 8 units/cc.	
VIII	B. pyocyaneus inhibited by 12 units/cc.	B. coli resistant to 50 units/cc. (Organism appeared during streptomycin treatment)

A mixed flora of gram-negative organisms is often seen in the superficial infections of the urinary tract which commonly occur following instrumentation. Streptomycin may be quite effective in eradicating the B. pyocyaneus from the urine although it usually is not uniformly successful in combatting all members of the group, (Cases VI, VII, VIII). However, the studies of Helmholz[144] show that some strains are among the most resistant of the organisms found in the urine. At least one of the mixture of organisms, usually B. coli in our experience, will often develop such pro-

nounced and rapidly increasing resistance to the agent that adequate treatment is not feasible. This factor is not as important with B. pyocyaneus as it is with B. coli, the resistance of which increases phenomenally during a short period of treatment. (Chart D.) This rapid change in susceptibility of the organism is not so evident in sulfonamide therapy, although it undoubtedly occurs to some extent. Thus such mixed infections will usually be greatly improved by elimination of some of the organisms, including B. pyocyaneus frequently, but will often not be completely cured. Three of the five cases reported here exhibited this phenomenon (VI, VII, VIII) while in one (IV) the urine was completely sterilized, at least temporarily, and in another (V) the whole group was resistant. These patients received 1 Gm. daily in divided doses every three to six hours intramuscularly for totals of 4 to 11 Gm. (except IV who had massive doses).

It is apparent from this small number of cases that streptomycin is a valuable addition to the limited number of agents which are effective against this organism, and that it may prove on further trial to be just as effective as the sulfonamides, if not more so. The striking lack of the characteristic histological findings at autopsy in Cases II and IV suggest that the streptomycin treatment exerted definitely beneficial effects even though these patients died. It is quite likely that strains which are resistant to one will be sensitive to the other so that the chances of cure in any infection are greatly enhanced by this addition.

Urethane and Sulfanilamide Solution. Recently good results have been reported in the treatment of local pyocyaneus infections with a solution of 10 per cent urethane and 1 per cent sulfanilamide applied directly to the areas every three hours. In a group of thirty-nine cases[145] there were fifteen in which the infections were caused primarily or in part by B. pyocyaneus, including chronic leg ulcers, chronic decubitus ulcers, infected surgical wounds and two instances of infected empyema cavities. When combined with adequate surgical drainage and/or débridement application of the mixture caused a disappearance of this organism from the infected areas in two to four days in the great majority, including one of the two cases of empyema.

In one of our cases (Case I) who received such treatment of the large decubitus ulcers locally combined with débridement the local response was excellent, although the necrotic areas were so large and her general condition was so poor that the prognosis was hopeless from the start.

Phenoxetol (β-phenoxyethylalcohol). In 2.2 per cent aqueous solution this substance has given good results in treatment of infected burns and superficial wounds.[146] When applied as constant soaks wet once daily the B. pyocyaneus was usually eliminated from the wounds in less than one week. B. proteus was more resistant, although frequently the wounds were also sterilized of this organism after a longer period of treatment. There was no effect on the gram-positive flora.

Acetic Acid. In 1 to 2 per cent solution acetic acid has been successfully used for many years in the treatment of superficial infections due to B. pyocyaneus, although some of the newer substances may be more rapidly efficacious. Taylor[147] found acetic acid dressings and soaks much more effective than a number of other medicaments, including Dakin's solution, in wound infections, and Rank[148] as recently as 1940 preferred it for treatment of infected granulating areas to be skin grafted.

COMMENTS

From consideration of the data presented the pattern of pyocyaneus infections is distinct. The organism is a gram-negative bacillus commonly found on the human

skin and infrequently in the normal gastrointestinal tract. It lacks invasive properties, hence its usual rôle is one of a relatively avirulent contaminant especially in superficial wounds in which it produces a characteristic blue-green pus. Sepsis and other serious infections due to this organism are definitely rare. However, because of the widespread use at present of penicillin, which efficiently removes gram-positive organisms and apparently promotes uninhibited growth of this and other gram-negative bacilli, the incidence of such important infections seems to be increasing. Case II, III, IV, IX and X are examples in whom it is probable that treatment with penicillin may have produced conditions favoring B. pyocyaneus invasion, or at least conditions which were ideal for rapid spread of such infection once a foothold had been established.

In addition to the usual manifestations several unique features serve to differentiate septic infections due to B. pyocyaneus from other types of sepsis. They occur almost exclusively in infants and children and in debilitated adults. Without exception our cases were in this latter group. Highly characteristic is the tendency to vascular involvement with thrombosis and infarction, resulting in production of ulcerating gangrenous areas in the skin ("ecthyma gangrenosum") particularly in the perineal and axillary regions, and in all sections of the gastrointestinal tract. Cases I, II and III exhibited these typical lesions, respectively, in the stomach, on the skin and in the rectum. The skin lesions and the large rectal ulcer were especially striking.

B. pyocyaneus sepsis is almost uniformly fatal, probably because of several factors. One of these is the tendency to occur in infants and children and adults with chronic debilitating disease which is so clearly shown in the literature and in our several cases. It is not surprising that in such individuals the mortality rate approaches 100 per cent; the almost universally fatal outcome is probably as much the result of the preexisting disease as it is of the superimposed pyocyaneus infection. Corroborating this is the good prognosis in the rare cases of persistent bacteremia simulating typhoid fever which generally occur in healthy individuals.

A second consideration in the prognosis is the resistance—original or acquired—of the strain of organism to the available chemotherapeutic agents. In the sulfonamides and streptomycin we have two quite promising drugs. Yet there is a large variation from strain to strain in sensitivity to both these substances, and a fair proportion is initially resistant. The lack of susceptibility to the two agents does not necessarily overlap, however, and a particular organism may be sensitive to one and resistant to the other, or vice versa. What is probably of equal importance is resistance in an originally sensitive strain developing rapidly during treatment, particularly with streptomycin. (Chart D.) An extreme example of such an occurrence was seen in Case III. Although from this and other studies it is apparent that the tendency to rapid development of resistance is seen more commonly with other organisms such as B. coli, this factor must have been an important reason in the failure of treatment in Case III. This phenomenon is a well known one; it occurs with many organisms and all types of chemotherapeutic agents. It can readily be produced *in vitro* and is an example of the ease with which bacteria can adapt themselves to an unfavorable environment.

Treatment, in this as in other infections, should be undertaken with these facts in mind. Since exposure to sublethal concentrations of the agent produces optimum conditions for development of resistance in the infecting organism dosage *from the beginning* should be adequate. In treatment

of pyocyaneus sepsis with streptomycin this means an initial dosage of 4 Gm. daily in divided doses every three hours intramuscularly. In urinary tract and other local infections 2 Gm. daily may be sufficient, although a resistant organism may necessitate a larger dose. In case of lack of response the resistance should be checked again using a freshly isolated organism. While streptomycin is still being administered cultures should be repeated frequently, not only of the blood but also of the nose and pharynx and other possible foci in an effort to detect in its incipiency a possible predominance of gram-positive pathogens. The development of serious infections with *gram-positive* organisms is already being noted in patients treated with streptomycin alone[149] and should be searched for carefully. In the event this occurs therapy with penicillin should not be delayed, meanwhile continuing the streptomycin administration.

SUMMARY

1. The literature on the various types of infection due to B. pyocyaneus is reviewed and ten cases are described in detail, including one case of endocarditis and one of pneumonia.

2. Local infections due to B. pyocyaneus are frequent and usually benign. The most common sites are superficial surgical wounds, the skin and the lower urinary tract. The organism is often seen as a secondary invader in chronic otitis media. Corneal ulcers are rare but important because of the tendency when untreated to progress to panophthalmitis.

3. The clinical picture in sepsis due to this organism is summarized from the literature and exemplified by four typical cases. Important features include the high mortality rate, tendency to occur in infants and children and in debilitated adults, and frequent occurrence of ulcerating gangrenous lesions in the skin ("ecthyma gangrenosum") and throughout the gastrointestinal tract.

4. In treatment the sulfonamides and streptomycin are the agents of choice. Streptomycin appears to be as good as, and in some instances, better than the sulfonamides, particularly in urinary tract infections. Factors which seem to be important in the lack of success of treatment with streptomycin in sepsis are the frequent presence of other serious disease producing general debility and occasional rapid development by the infecting organism of resistance to the chemotherapeutic agent. For local infections applications of 1 to 2 per cent acetic acid have been known to be efficacious for many years. Recently good results have been obtained in such conditions by the use of phenoxetol and of a solution containing 10 per cent urethane and 1 per cent sulfanilamide.

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Seminars on Rheumatic Fever

Clinical and Laboratory Diagnostic Criteria of Rheumatic Fever in Children*

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It is the purpose of this seminar to present the clinical manifestations of rheumatic fever as seen in a large group of children six to sixteen years of age. The natural course of the disease in this group of children was uninfluenced by therapy, as no medication was administered to this group. The treatment consisted of bed rest and balanced diet and occasional sedation for pain or restlessness. It is the further aim of this discussion to present and evaluate the laboratory aids currently used in arriving at a diagnosis of rheumatic activity. The emphasis will be placed upon evolving a clinical picture of the disease as we see it at a sanatorium where the course of the disease may be followed closely and in detail.

PART I. CLINICAL MANIFESTATIONS

A full description of the classical clinical manifestations of rheumatic fever fails to give an adequate picture of the disease. The text book procedure of describing the most striking signs and symptoms of the disease has failed to give due emphasis to the more elusive, yet more important manifestations from the point of view of prognosis. Acute polyarthritis and obvious evidence of valvular disease, for example, occupy more attention in the literature of rheumatic disease than does mild progressive carditis or the poorly recognized visceral manifestations of the disease. The latter, in our experience, constitute prognostically the more important features of rheumatic fever.

These clinical manifestations may be divided into several categories: (1) those that are an expression of the toxicity of the illness; (2) those that are significant of a disturbance in the supporting and nervous structures of the patient; (3) those that speak for manifest rheumatic disease of the visceral structures.

It is clear, however, that although these three categories are distinct, they overlap from time to time or manifest themselves simultaneously. The dominance of one group of manifestations over another, in our experience, is an expression of the individual patient's adaptation to the disease. In this regard age, sex, social status, geographical location and heredity may play a significant rôle. Some manifestations are more common in early childhood; others in adult life. The same manifestations may express themselves somewhat differently at different age levels or in different localities. The important features of the disease, however, are that it is protracted, universal in its distribution in the organism, self-perpetuating and eventually self-limited. These characteristics are uninfluenced by age, sex, color, et cetera. Joint manifestations, for example, are more common and more refractory to treatment in the adult. Chorea, on the other

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hand, rarely occurs after adolescence. Rheumatic carditis is more often recognizable in the child but on closer examination will be found to exist in the adult as well but perhaps in a more elusive form.

A. MANIFESTATIONS WHICH ARE AN EXPRESSION OF THE TOXICITY OF THE DISEASE

1. *Fever.* Low-grade fever in rheumatic patients has always been looked upon as indicative, with high probability, of rheumatic activity. A flat temperature curve is commonly relied upon by most physicians as a sign of the cessation of the active rheumatic process. Experience with rheumatic children shows that "fever alone is a common erroneous basis for a diagnosis of rheumatic fever."[1] Our observations indicate that all cases of acute rheumatic disease show a mild febrile course for the first one to six weeks. Occasionally, a child will continue to have a low-grade temperature for as long as twelve weeks. Actually, only one-fifth of the patients, in our experience, have a low-grade fever after the fifth week. It is of some significance to note that all patients during the febrile period of the disease show obvious signs of active rheumatic disease but the great majority (90 per cent) continue to demonstrate rheumatic activity after the temperature is completely normal. (Fig. 1B.)

It is to be remembered that many children have a normal temperature range of 99° to 100°F. (37.3° to 37.8°C.) It is deplorable to think that many a child has been sent away from home with a diagnosis of rheumatic fever simply on the basis of a low-grade temperature, without any other manifestations. It cannot be emphasized too strongly that fever as a single manifestation of rheumatic disease is an unreliable criterion of rheumatic activity.

2. *Failure to Gain Weight.* For some time, a consistent gain of weight has been considered indicative of the onset of the quiescent phase of rheumatic fever.[2] Our observations show that more than one-half of the children are either normal in weight or above normal at the beginning of the rheumatic episode. All of these children show a slight loss in weight during the first eight to nine weeks of the active disease but by far the vast majority (85 per cent) begin to gain weight after the ninth week following the onset of active rheumatic disease. In our group of cases, two of every five children continue to show mild rheumatic activity although they had reached a normal weight gain level. (Fig. 1F.) A return to normal weight gain level of the patient cannot, therefore, be used as a criterion for the cessation of rheumatic activity.

3. *Appearance and Behavior of the Patient.* Clinicians have observed for many years that the rheumatic patient presents a typical appearance during the acute phase of the disease. His pallor has been described in various ways and has been considered typical of the acute process. It has been observed that the pallor is far greater than one would expect from the level of hemoglobin. It has further been noted by pediatricians and students of rheumatic disease that the child suffering from rheumatic activity shows a high degree of emotional instability. His appetite is capricious. His sleep is restless. His habits of evacuation and urination are disturbed. Marked and frequent fluctuations of expressions of elation and depression are commonly observed during the active phase of the disease. Easy fatiguability in active rheumatic patients is a common occurrence. The child who under normal circumstances is anxious to participate in childhood activities, during the mild active disease devises ways and means of substituting less vigorous and in some instances completely circumscribed activity, provided he is given a chance to do so.

These clinical manifestations as expressed

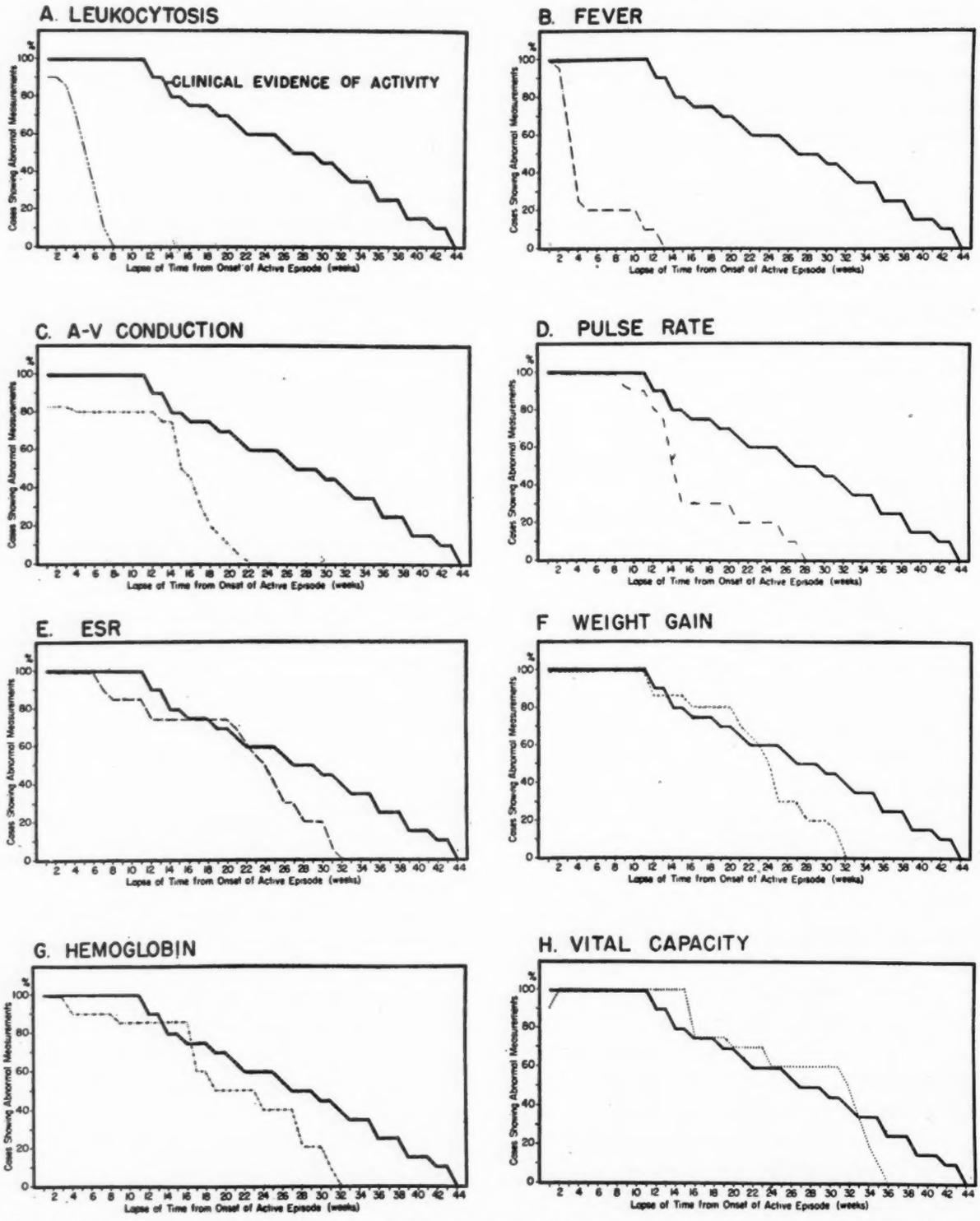

FIG. 1. Per cent of cases showing abnormal laboratory and clinical measurements in relation to lapse of time from the onset of the active episode. (Courtesy of *J. Pediat.*, 29: 77–89, 1946.)

in the appearance and behavior of the patient are indeed very often the only signs of rheumatic activity and, in our experience, may be relied upon as important criteria for the diagnosis of active rheumatic disease.

B. MANIFESTATIONS SIGNIFICANT OF DISTURBANCE IN THE SUPPORTING STRUCTURES AND NERVOUS SYSTEM

1. *Joint and Muscle Pain.* In rheumatic children, arthralgia and myalgia are not often clearly defined. A careful history will reveal that the majority of young rheumatic children complain of muscle and joint pain in the lower extremities. A detailed analysis of these complaints, however, brings into clear relief a distinct classification of these complaints from the point of view of diagnosis. Many rheumatic children complain of joint and muscle pains but these are unrelated to the rheumatic diathesis. In our experience, such complaints occurring at night and relieved by the application of heat are almost always significant of "growing pains" and do not constitute one of the symptoms of rheumatic disease. Similar symptoms occurring during the course of physical activity in a rheumatic child are in most instances significant of rheumatic disease. When such complaints are continuous and uninfluenced by the application of heat or light massage, other clinical and laboratory criteria of rheumatic activity are usually discovered on careful examination. But when these complaints are evanescent and are clearly associated with fluctuations in the weather, other criteria are not found as a rule although there is evidence to show that this type of arthralgia or myalgia is a characteristic complaint in quiescent rheumatic disease.

It is, therefore, of considerable importance to distinguish between growing pains, the joint and muscle pains of the quiescent rheumatic patient, and those associated with rheumatic activity. In our experience, the latter occur in three of every four patients suffering from rheumatic disease if a careful history is taken.

Migratory polyarthritis has been considered by many as the most common and typical manifestation of rheumatic fever. In children this syndrome is not too impressive. It does not occur as frequently as in the adult. In our experience, rheumatic fever in children is diagnosed more frequently in the absence of polyarthritis. Indeed, when this syndrome occurs it offers considerable difficulty in diagnosis. It is not always clearly separated from rheumatoid arthritis, serum sickness and other allergic joint manifestations. In fact, it is hazardous to make a diagnosis of rheumatic disease in children on the basis of polyarthritis alone. It has been stated by some quarters that migratory polyarthritis which follows a beta hemolytic streptococcal infection or scarlet fever should be considered as of rheumatic origin. Our observations in children do not always concur with this contention. We have not been convinced that when polyarthritis occurs as a single manifestation following a beta hemolytic streptococcal infection, the diagnosis of rheumatic fever is always substantiated. Many such cases do not present other rheumatic manifestations in their follow-up history. We are rather impressed with the finding that rheumatic polyarthritis in children is always associated with other criteria for the diagnosis of rheumatic fever; that the absence of other criteria puts the diagnosis of rheumatic polyarthritis in doubt. Our evidence further shows that all children with definite rheumatic polyarthritis not only present clinical and laboratory evidence of rheumatic disease but few indeed escape obvious cardiac damage. This becomes manifest on careful physical examination. Furthermore, the "rule" that rheumatic polyarthritis is always temporary and reacts favorably to salicylate therapy

cannot be relied upon in making a diagnosis of rheumatic disease. While it is true that most patients can be controlled rapidly and completely by appropriate therapy, those which are not relieved by salicylate therapy and are of long duration may nevertheless be of rheumatic origin. In addition, many cases with toxic and allergic joint manifestations are frequently temporary in nature and are often favorably influenced by salicylate therapy. Our evidence, therefore, would seem to show that emphasis must be placed upon finding other clinical and laboratory criteria of rheumatic activity before a diagnosis of rheumatic polyarthritis can be established.

2. *Skin and Mucous Membranes.* The skin manifestations of rheumatic disease take on various characteristics (erythema annulare, marginatum, and nodosum). Erythema marginatum is considered by most students of rheumatic fever as a typical manifestation. It is always associated with other signs and symptoms of rheumatic disease and most frequently, in our experience, with the visceral type of rheumatic activity. This cutaneous manifestation may be evanescent or lasting; it may be widespread or localized. It is not associated with discomfort or itching. It is always associated with carditis. Similarly, subcutaneous nodules always establish the diagnosis of rheumatic activity. These occur late in the disease and are also always associated with acute carditis. The incidence of nodules in rheumatic patients is proportional to the care with which they are searched for. The larger nodules are clearly defined and usually occur on the bony prominences. These are not missed as often as those that are attached to the tendon sheaths, deep fascia and superficial aponeuroses. Only detailed observation and palpation is rewarded by the finding of these small nodules.

The prognostic significance of subcutaneous nodules and erythema marginatum has been discussed for many years. In our experience, erythema marginatum occurs in patients who have well advanced rheumatic disease. Rheumatic nodules are always associated with severe and protracted heart disease. In these instances, they have been looked upon as indicative of a poor prognosis. In some quarters, on the other hand, rheumatic nodules are considered an expression of the stage of proliferation or healing; hence, a favorable prognostic sign. Statistical analysis of our clinical material fails to assign a distinct prognostic significance to the occurrence of rheumatic nodules. Some children having numerous and universally distributed crops of nodules recover from an acute rheumatic bout and seem to present a good outlook for the future. Other patients develop subcutaneous nodules in the terminal stage of the disease.

Epistaxis: Nose bleeds are common in children suffering from rheumatic disease. Occasional non-traumatic and non-irritating mild epistaxes occur more frequently in rheumatic than in non-rheumatic children, but do not always signify rheumatic activity. Bouts of profuse epistaxis of sudden onset, however, are always associated with active rheumatic carditis in rheumatic children. Cauterization of the nasal mucosa in the first group is always successful in stopping epistaxis; in the second group during the course of active rheumatic disease, cauterization frequently fails to control the bleeding. It must be said that exsanguinating nasal bleeding is not seen as frequently now as described in the older texts on rheumatic disease. The reason for this is not clear. In the course of nine years experience at a sanatorium where hundreds of children have been observed for many months during the course of rheumatic activity, the nasal tray has been used only on rare occasions.

3. *Central Nervous System.* Little has been added to the clinical picture of chorea since the time of Sydenham. This clinical picture,

however, is descriptive only of the explosive phase of chorea and does not clearly define its relationship to the rest of the rheumatic syndrome complex. Our observations seem to show that: (1) Chorea as a rheumatic manifestation begins months in advance of the obvious muscular incoordination. Emotional instability, restlessness, capriciousness, and other less obvious personality changes are always apparent many weeks before actual bizarre choreiform movements begin. In addition, such personality deviations continue in many instances for years following "acute" chorea. (2) Nearly one-half of the cases of chorea are associated with other rheumatic manifestations. While carditis, rheumatic pneumonia, nephritis, hepatitis and other visceral manifestations are not frequently seen in cases whose dominant rheumatic manifestation is chorea, the incidence of valvular disease in so-called "pure" chorea is only slightly lower than in those whose dominant manifestation is polyarthritis. The distinct difference between the two groups is in the duration of the evolution of the valvular disease. Chorea cases must be observed for many years before cardiac damage becomes manifest. (3) Chorea rarely appears in the adult and is therefore of little diagnostic value in rheumatic disease in the adult. It seems to be more common in girls and sometimes recurs during the pregnant state.

C. VISCERAL RHEUMATISM

1. *Respiratory System.* The significance of rheumatic bronchitis has not been sufficiently stressed in the medical literature. In our experience, it is prognostically one of the most important manifestations of visceral rheumatism. Children who present signs of bronchitis during the course of rheumatic activity do not do well as a rule. Therapy directed toward the relief of cardiac decompensation or toward the relief of bronchial spasm does not produce the expected results. These cases are always associated with severe carditis and are frequently observed in the terminal stage of the disease. It is of some importance to note that oxygen therapy, which is often a life saving measure in rheumatic carditis in our experience, is contraindicated in the bronchitic type of rheumatic disease. A concentration of as low as 50 per cent oxygen almost immediately produces severe asthma with urgent air hunger, cyanosis, restlessness, profuse perspiration and striking expression of anxiety. In all of these cases it becomes necessary to terminate oxygen therapy at once to avoid a catastrophic outcome.

Rheumatic pleurisy is a much more common finding in children with rheumatic activity than would appear from the medical literature. More than half of the cases of rheumatic pleurisy can be diagnosed only by careful roentgenographic study. Many of these cases present indefinite and bizarre types of pain in the chest frequently considered as being due to pericarditis or to coronary insufficiency. Others have typical pleuritic pain which, however, is evanescent and easily controlled with appropriate doses of salicylates. Still other cases have classical pleuritic signs often missed if examinations are not frequent. Our evidence does not seem to indicate a correlation between rheumatic pleurisy and prognosis.

From time to time the term "pneumonitis" is used to describe pneumonic signs which are spotty and temporary. Consonating râles are heard chiefly at the bases and the infrascapular region; rarely dullness and tubular breath sounds are observed in these cases. These findings may change from day to day and may completely subside in twenty-four to thirty-six hours. They are always associated with carditis and are not related to the advent of congestive failure. *X*-ray examination of the lungs does not disclose any definite consolidation but often

shows an unsuspected interlobar pleural thickening.

The specificity of rheumatic pneumonia has been debated for many years. The clinical picture in children is that of lobular pneumonia associated with rheumatic carditis. There is a marked increase in respiratory rate. Dullness, crepitant râles and bronchial breath sounds are heard in various and scattered areas of the chest. These signs may appear and disappear from day to day but often persist for longer periods. The dominant clinical picture, in our experience however, is that of carditis and not of pneumonia. There seems to be no correlation between the degree of carditis and the occurrence of pneumonia. It is well to remember that rheumatic pneumonia is not favorably influenced by the use of antibiotics or the newer chemotherapeutic agents. Massive doses of salicylates seem to be of more specific help. Unfortunately, however, salicylate hyperventilation is a common occurrence in rheumatic pneumonia. Great care must be taken, therefore, to differentiate between the tachypnea of pneumonia and the hyperventilation of salicylate intoxication.

2. *Digestive System.* Abdominal pain is a frequent complaint in rheumatic children and if clearly delineated is significant of rheumatic activity. This abdominal colic may vary from occasional slight spasmodic para-umbilical pain to severe pain and tenderness simulating an acute surgical condition of the abdomen. Frequently, the symptom complex is indistinguishable from acute appendicitis and the differential diagnosis becomes difficult or impossible. These cases present not only exquisite tenderness and spasm over McBurney's point, but also distinct tenderness in the appendicular region on rectal examination. It is well to remember, however, that there are rarely concomitant symptoms of acute appendicitis in these children. Constipation, diarrhea, anorexia, nausea and vomiting are not usually observed in these cases. We found that a moderate dose—20 to 30 gr. (1.2 to 2 Gm.) of sodium salicylate given intravenously often helps in the differential diagnosis in such instances. The "acute abdomen" subsides within a few hours after the salicylate level of the blood is raised.

Abdominal pain in a rheumatic patient is often referred pain from an acute fibrinous pericarditis, perihepatitis or perisplenitis. In these cases, salicylate therapy does not usually produce the expected favorable results. Cardiac fatigue occasionally produces abdominal pain. Finally, the occasional association of abdominal periarteritis nodosa with rheumatic heart disease must be kept in mind in the differential diagnosis of abdominal pain in a rheumatic patient.

Enlargement of the liver associated with vague digestive complaints is a frequent finding in rheumatic activity in children. This is always associated with acute carditis but is not, in our opinion, an expression of heart failure. The liver edge may indeed be palpable as low as the umbilicus but more often is only one or two fingers below the costal margin. The liver edge is soft and slightly tender. The epigastric distress is out of proportion to the enlargement of the liver. Dehydration therapy does not decrease the size of the liver in these cases. The liver edge recedes only when rheumatic activity subsides. Our evidence shows that an enlarged liver in the absence of signs of right heart failure is always significant of protracted rheumatic activity of a high degree of severity and is always associated with acute carditis. The prognosis in these cases is not a favorable one.

3. *Rheumatic Nephritis.* Most of our patients with acute carditis show more than occasional red blood cells in the urine and some an occasional granular cast. These findings are not limited to those with evidence of incipient or definite heart failure.

Detailed and careful urine examinations do not disclose sufficient evidence to make a diagnosis of nephritis. Occasionally, typical urinary findings of acute glomerulonephritis are observed. It is not clear from our observations whether these cases represent a specific rheumatic nephritis or superimposed nephritis of other origin. The clinical course is not unlike that of any acute nephritis. Some cases are associated with moderate hypertension. The majority do not present any sequellae and have not been found to develop chronic nephritis.

In rare instances, a specific nephritic syndrome occurs in rheumatic children, i.e. "renal epistaxis." The patient develops profuse bleeding from the kidney. The hemoglobin and red blood cell count drop rapidly, producing a severe secondary anemia. Thus, in a period of forty-eight hours, the patient's hemoglobin may drop from 12 to 4 Gm. This "renal epistaxis" is most frequently found in rheumatic patients who are subject to bouts of nasal epistaxis. On rare occasions it becomes necessary to administer transfusion. This procedure, and this procedure only, will in some instances stop the severe renal bleeding. Once the bleeding has ceased, the patient makes a rapid and uneventful recovery without evidence of chronic renal disease. Renal epistaxis, in our experience, is always associated with acute rheumatic carditis. It does not present the clinical picture of renal embolization. It is associated with severe reactivation of the rheumatic process rather than with significant alteration in cardiac function and the advent of heart failure.

4. *Acute Rheumatic Heart Disease.* Of greatest importance both from the point of view of diagnosis and of management is acute carditis. While the clinical and pathologic relationship of acute heart disease and rheumatic fever was demonstrated conclusively by Bouillard more than a century ago, the diagnosis and prognosis of rheumatic heart disease has been based almost entirely until recent years upon the state of the valves. As late as 1924, Cohn and Swift stated that it was not possible to say during the acute stage of rheumatic fever, "whether heart disease is likely to be established."[3] They were of the opinion at that time that only long after the acute episode of rheumatic disease had subsided could the diagnosis of heart disease be made.

In recent years, interest has moved from the study of valvular damage to that of acute heart disease. It has become apparent to most clinicians that carditis is the most frequent, the most insidious, and the most damaging manifestation of rheumatic fever. The signs of valvulitis and obvious pancarditis are easily recognizable and have been so well described in the medical literature that they need no further discussion here. It is the mild case of carditis that is troublesome from the point of view of diagnosis. It is this manifestation of rheumatic disease that needs further description and illustration. In our experience, rheumatic carditis in children is almost synonymous with rheumatic activity since few patients having active rheumatic disease can be declared not to have acute carditis.

Despite the great increase in knowledge of the natural history of rheumatic disease and its cardiac manifestations, no criteria have been forthcoming for the diagnosis of rheumatic carditis, when this manifestation is mild. We are impressed with the fact that children having rheumatic carditis present two sets of manifestations: (1) those concerning the general appearance of the patient, and (2) those describing the disturbance in cardiac function as determined by auscultatory examination and cardiographic study of the electrical sequence of events in the cardiac cycle.

As mentioned above, a child who under normal circumstances is anxious to participate in all childhood activities devises ways

and means for substitution of less vigorous and in some instances completely circumscribed activities during the course of mild active rheumatic carditis. During this phase the child is emotionally unstable. He is restless; his appetite is capricious; he presents mild gastrointestinal upsets. There is also a bizarre reaction to his environment; at times he is overly exuberant and at other times falls into a pronounced depressive state. The child is pale and looks more ill than the physical findings would seem to dictate. Increase in physical activities or emotional disturbance accentuates his appearance of illness. It is of some importance to note that as long as rheumatic carditis continues this typical pallor continues.

For many years, frequent and distinct changes in cardiac sounds and murmurs have been considered significant of mild carditis. We are impressed with the fact that the volume and pitch of the first heart sound varies from day to day and often from beat to beat. Murmurs change in quality, direction and extent of transmission. It would seem that the cardiac dynamics responsible for cardiac sounds and murmurs are in a state of flux in active carditis, and stabilize when the disease becomes quiescent. Most clinicians have recognized that in acute rheumatic fever tachycardia with a tumultuous rhythm is significant of carditis. Some believe that rapid increase in cardiac size, (i.e., cardiac dilatation and hypertrophy), increase in the extent of valvulitis, and rapidly advancing signs of cardiac insufficiency—all these are criteria of rheumatic carditis, and the absence of these manifestations has been considered as reliable evidence that active carditis has subsided.

In the last few years, we have come to consider changes in cardiac rhythm as a more sensitive and dependable sign of active carditis. It has been our observation that the cardiac rhythm in acute carditis simulates an embryocardia, irrespective of the cardiac rate. The usual 1:2 rhythm heard in normal hearts at a slow rate is completely lost in acute carditis and more nearly approaches a 1:1 rhythm. The interval between the first and second heart sounds is equivalent to or longer than that between the second and first. This type of rhythm is not modified by the cardiac rate as long as acute carditis continues.

It is only when active rheumatic disease subsides that this specific disturbance in cardiac rhythm gradually returns to normal. The period during which restoration to the normal 1:2 ratio occurs is of long duration in most cases. Careful auscultatory examination reveals that complete physical and emotional rest in a patient with acute rheumatic disease approaching the quiescent stage may present a normal cardiac rhythm which, however, is easily disturbed when physical and emotional disturbance occurs. The nearer the patient approaches the quiescent state, the less pronounced is this disturbance during physical or emotional exertion. When, however, the usual physical and emotional activities fail to cause a disturbance in the systolic-diastolic sequence of events as described, rheumatic activity in the heart muscle, in our experience, very likely is at an end.

Thus, it has become clear from careful and detailed observations of large groups of children with rheumatic carditis that the unstable character of the cardiac rate, the ever changing heart sounds and murmurs, and the disturbance in relationship of systole to diastole constitute the primary criteria for rheumatic carditis. Our experience has shown that when children who present these criteria, even if all other laboratory signs of rheumatic activity have become normal, are permitted to assume normal physical activities, signs of rheumatic reactivation and progressive cardiac damage are certain to

become manifest within a short period of time. (Table 1.)

TABLE 1
EFFECT OF PHYSICAL ACTIVITIES UPON RHEUMATIC CARDITIS

Patients	No. of Patients	No. of Reactivations	Percentage Increase in Cardiac Enlargements
Children who received complete bed rest during entire period of rheumatic carditis.	55	2	4
Children who were permitted limited physical activities when all criteria of rheumatic carditis have subsided except a prolongation of the Q-T interval.....	50	26	11

Acute pericarditis as a manifestation of rheumatic heart disease has been described repeatedly and needs no further discussion here. It is significant, however, that careful and repeated examinations of children having acute rheumatic disease will demonstrate the occurrence of fibrinous pericarditis more often than would appear from the literature. Three of every four children with acute rheumatic heart disease exhibit a pericardial friction rub at some time during the course of the disease. It is also of some importance to note that pericarditis with effusion is, in most cases, favorably influenced by massive salicylate therapy. In our experience, thoracentesis is rarely necessary.

SUMMARY OF CLINICAL MANIFESTATIONS

It appears, therefore, that rheumatic fever in children expresses itself in various ways depending upon the spread and severity of the rheumatic process. It may affect any part of the body, visceral as well as the supporting structures. From our experience with rheumatic children it would seem clear that from the point of view of both diagnosis and prognosis, emphasis should be placed upon the visceral manifestations rather than upon joint, skin or central nervous system signs and symptoms. Joint manifestations, skin manifestations and chorea are expressions of short explosive phases of a long-standing disease and do not help in deciding as to when rheumatic activity begins or ends. Careful observation of the patient as a whole and more detailed study of the disturbances of the function of his heart are rewarded by a more accurate diagnosis of rheumatic activity.

The clinical manifestations of rheumatic disease which dominate the scene may differ from patient to patient. This, in our experience, depends in the main upon the age of the patient. We believe, however, that in most instances rheumatic activity very likely continues for the greater portion of the childhood years; that the clinical manifestations which have been described are simply expressions of the explosive phases of the disease; and that so-called subclinical rheumatic activity goes on even in the absence of these clear-cut clinical manifestations. (Fig. 2.)

We have come to consider evidence of disturbance in cardiac function as one of the most important signs of rheumatic activity. Further progress in diagnostic criteria of mild rheumatic carditis would be helpful in arriving at a decision when rheumatic activity begins or finally comes to an end.

PART II. LABORATORY CRITERIA OF RHEUMATIC ACTIVITY

In recent years many laboratory tests have been proposed to measure rheumatic activity. It must be admitted that some of these tests have won confidence in the mind of the general practioner as a means for determining when the disease is no longer active. Clinicians and students of rheumatic fever are aware of the fact that none of these

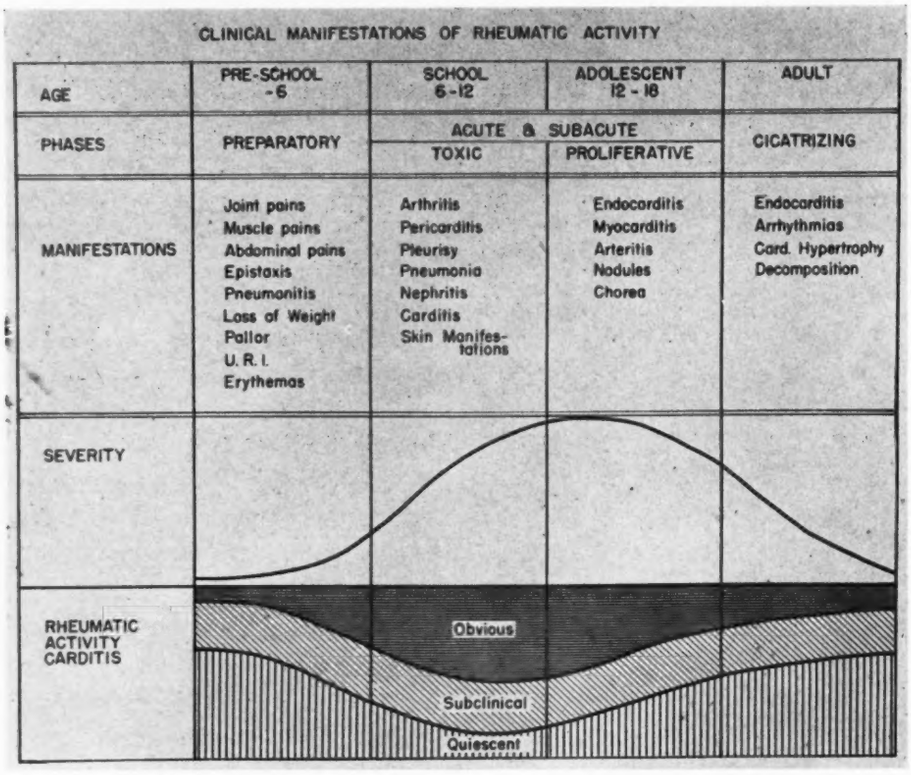

FIG. 2. Schematic representation of the usual clinical rheumatic manifestations and percentage incidence of rheumatic activity in the form of carditis in relation to the age of the patient. "Obvious" represents the usual text book signs and symptoms of carditis. "Subclinical" represents evanescent clinical and electrocardiographic evidence of carditis in the absence of the usual laboratory criteria of rheumatic activity. "Quiescent" represents all other cases that do not show any evidence of rheumatic activity. The curve opposite "Severity" represents the degree of carditis encountered. One plus severity: patients who present laboratory evidence of rheumatic activity and, in addition, present the clinical criteria of cardiac involvement; that is, changing heart sounds and murmurs, labile cardiac rate and fatigability. Two plus severity: patients who, in addition to the foregoing findings, show definite cardiographic evidence of conduction disturbance or/and changes in the ventricular complexes. Three plus severity: patients who, in addition to the foregoing, present a tumultuous heart with moderate symptoms of impaired cardiac reserve. Four plus severity: patients with acute pancarditis.

tests, singly or in combination, can serve as an adequate screening method of rheumatic activity. Yet many are inclined to consider these tests pertinent "in evaluating the presence of active rheumatic fever."[1]

Our experience seems to show that none of the currently used laboratory measurements can be used as specific diagnostic criteria for active rheumatic disease. This conclusion is based upon evaluation of laboratory tests done upon a large group of rheumatic children who were observed daily from the very onset of the active episode and for many months following obvious rheumatic activity.

LEUKOCYTOSIS

The value of the leukocyte count as an index of rheumatic infection in children has been discussed for more than two decades.[4] Some observers found it helpful in the classification of the degree of rheumatic activity.[5,6]

One in every ten of our cases showed no elevation of the white blood count at any time during the entire course of active rheumatic carditis. Nine of every ten showed a leukocytosis during the first two weeks of the illness, and seven of every ten continued to show such elevation at the end of the fourth week. No leukocytosis was observed in any of our cases after the seventh week after onset of the active episode. All our cases with leukocytosis at the onset showed a definite decline in the total white blood count with lapse of time. It is significant that while all cases with leukocytosis had obvious manifestations of clinical rheumatic activity, nine of every ten cases continued to show clinical evidence of active rheumatic disease after the total white blood count had returned to normal. (Fig. 1A.)

PULSE RATE

An increase in the pulse rate out of proportion to the elevation of temperature is a frequent finding in acute rheumatic fever. Thus, children who have a temperature of 101° to 102°F. (38.4° to 38.9°C.) may have an average pulse rate of 140. Similarly, other children whose temperature is normal may continue to have a pulse rate of 120 to 130 when rheumatic activity is present.

In the first three weeks after the onset of illness the pulse rate in our group of cases was found to be higher than at any other time thereafter. None of the patients showed a pulse rate of less than 100 before the end of the ninth week from onset of the acute episode, and none had an elevated pulse rate twenty-seven weeks after the onset. The most marked decline in pulse rate was observed at the beginning of the tenth week.

It is noteworthy that four of ten children whose pulse rates remained normal continued to show clinical evidence of active rheumatic disease. On the other hand, a few cases who were apparently quiescent showed occasional sinus tachycardia. (Fig. 1D.)

SEDIMENTATION RATE

It is generally appreciated that an increase in the erythrocyte sedimentation rate is found in most toxic and infectious diseases. In rheumatic disease, an increase in the erythrocyte sedimentation rate has been considered as the most useful finding in evaluating the presence of rheumatic activity, and some observers are inclined to look upon it as of specific diagnostic, as well as prognostic, significance in rheumatic fever.[7–13]

In our group of cases, the sedimentation rate was not as good a guide of rheumatic activity as is commonly reported. Many cases had definite active rheumatic disease with a normal sedimentation rate. No evidence of heart failure was observed in this group. All children showed marked elevation during the first eight weeks from the onset of the illness, the elevation being most marked during the first four weeks. At the end of eight weeks, 15 per cent of the cases had normal sedimentation rates but many of these continued to show evidence of active rheumatic disease. After the twentieth week, an increasing number of children showed a normal sedimentation rate, and at the end of thirty-two weeks, the sedimentation rate became normal in all the cases although 40 per cent of the group still showed some clinical evidence of mild rheumatic activity. (Fig. 1E.) Of equal significance is the fact that at the end of the sixteenth week, a number of children who failed to show clinical evidence of rheumatic activity had a slightly elevated sedimentation rate.

HEMOGLOBIN

Secondary anemia is usually present during rheumatic activity, the degree of anemia being related to the severity and duration of the manifestations of the disease. It is considered a characteristic finding during active rheumatic carditis.[14–17]

All our patients showed a moderately severe anemia at the onset of the acute episode. During the first week, the hemoglobin ranged between 7 and 9 Gm. for the entire group. From the end of the first to the end of the fourth week, there was a further depression in the hemoglobin level so that at this time the range was only 7 to 8 Gm. At the end of the fourth week, two of the children showed a hemoglobin of 5 Gm. It was only twelve weeks after the onset of the illness that thirty of the children, or about 15 per cent, showed a hemoglobin of 12½ Gm. or more. Twenty-four weeks after the onset, half of the children had a normal hemoglobin level. It was only thirty-two weeks after the onset that the hemoglobin of all the children had returned to 12½ Gm. or more.

It may be said, therefore, that in our group of cases none showed a normal hemoglobin at the beginning of the illness; the lowest hemoglobin level was found in the period from the second to the fifth weeks of illness; and all the children showed a normal hemoglobin eight months after the onset of the illness. In a great many instances, the hemoglobin did not return to normal until the activity had subsided. On the other hand, 40 per cent of the cases showed clinical evidence of rheumatic activity after the hemoglobin had returned to normal. (Fig. 1G.)

VITAL CAPACITY

It is generally agreed that a diminishing vital capacity is one of the earliest signs of left ventricular failure. It has been suggested that a low vital capacity in a rheumatic patient is to be considered a good index of rheumatic activity in the heart muscle when all other factors which might influence the vital capacity are excluded.[18,19] Reduction of the vital capacity in a rheumatic patient is looked upon as a measure of left ventricular failure even in the absence of the more obvious signs and symptoms of cardiac insufficiency.

In our experience, the vital capacity seems to be one of the most sensitive criteria of the progress of active rheumatic disease. All children during the active phase of the disease showed a vital capacity of 40 per cent or more below normal for age and body surface. Children below eight years of age were excluded from this group since the vital capacity reading is unsatisfactory at this age level.

For the first three months of rheumatic activity, none of the children showed a rise in vital capacity. Some began to have a slight increase three months after the onset of activity. The rise was small and the number of cases few. After the first three months, more cases showed a gradual rise in vital capacity, but none reached normal for age and body surface until sixteen weeks following the onset of rheumatic carditis. At this time, one in every four children had a normal vital capacity. The last case which returned to normal vital capacity reading was eight and a half months after the onset. On the other hand, even after this lapse of time one-quarter of the cases still showed mild clinical evidence of rheumatic activity. (Fig. 1H.) Thus, while the vital capacity was the last measurement to return to normal, it failed to be a specific diagnostic measurement, as many of the cases continued to show clinical evidence of active rheumatic disease while having a normal vital capacity. Some few children had a low vital capacity but failed to show clinical evidence of rheumatic active disease on repeated examination.

ROENTGENOGRAPHIC CRITERIA

It has been our experience that obvious cardiac enlargement as measured by *x*-ray and fluoroscopy occurs mainly during the course of active rheumatic disease. Thus, most of our cases irrespective of the degree of

valvular damage were shown to have active rheumatic disease when careful chamber studies were made for evidence of even the slightest increase in cardiac size. On the other hand, many of our cases who could not be convicted on clinical or laboratory evidence as having active rheumatic disease did not demonstrate progressive cardiac enlargement over long periods of time although they presented advanced valvular disease.

ELECTROCARDIOGRAPHIC CRITERIA

Much has been written on the subject of cardiographic findings in rheumatic disease. Obviously, no clear-cut findings have been described as specifically diagnostic of rheumatic disease. Histologic evidences of cardiac damage in this disease are universal in their distribution and vary in degree from a mimimal inflammatory process to complete disorganization of the heart muscle, its endocardium and conduction system. While the conduction system has been considered particularly vulnerable to rheumatic disease, no cardiographic finding significant of conduction disturbance has been found to be specific for rheumatic disease.

Some electrocardiographic changes become fixed and cannot therefore be used as criteria for active carditis. Most electrocardiographic abnormalities described in the literature demonstrate evidence of temporary ischemia or permanent scar formation of the cardiac muscles. Most studies attempt to correlate electrocardiographic findings with the histopathology known to exist in myocarditis and few of these studies take into clear account the pathologic physiology mirrored in the cardiogram in the acutely inflamed heart muscle.

1. *A-V Conduction.* The finding of prolonged auriculo-ventricular conduction time in a rheumatic patient has come to be regarded as evidence of rheumatic carditis even in the absence of other laboratory or clinical evidence of rheumatic disease, and many a patient has been thus stigmatized as long as his P-R interval has remained prolonged. On the other hand, a return of the P-R interval to normal is looked upon with confidence as a sign of cessation of rheumatic activity.

A significant number of our cases (17 per cent), did not show any prolongation of the A-V conduction time at any time during the entire course of the active rheumatic process. It is probable that some of these might have shown a prolongation of conduction time had electrocardiograms been taken at more frequent intervals. Ninety-nine per cent of the children who had prolonged auriculo-ventricular conduction time at the onset of the carditis showed a normal conduction time later. However, a large proportion of the cases showed clinical evidence of rheumatic active disease when the auriculo-ventricular conduction time had returned to normal. It is of some significance that two cases gave the impression of cessation of active rheumatic disease although the auriculo-ventricular conduction time was still prolonged. Both of these cases showed the same conduction time two years after cessation of activity. (Fig. 1c.)

2. *Precordial Leads.* The addition of precordial leads has increased the incidence of abnormal cardiographic findings in rheumatic fever. Lead IV was found of clinical value as an aid in recognition of myocardial involvement in rheumatic fever; successive changes in the S-T segment and the T waves were interpreted as showing that the cardiac lesions were not in a quiescent state.

3. *Prolongation of Electrical Systole (Q-T Interval).* The impression gained from careful auscultation of the hearts of children suffering from acute carditis is that there is a distinctive disturbance in the normal sequence of events in the cardiac cycle as regards the length of systole in relation to diastole. In order to test this thesis, we have

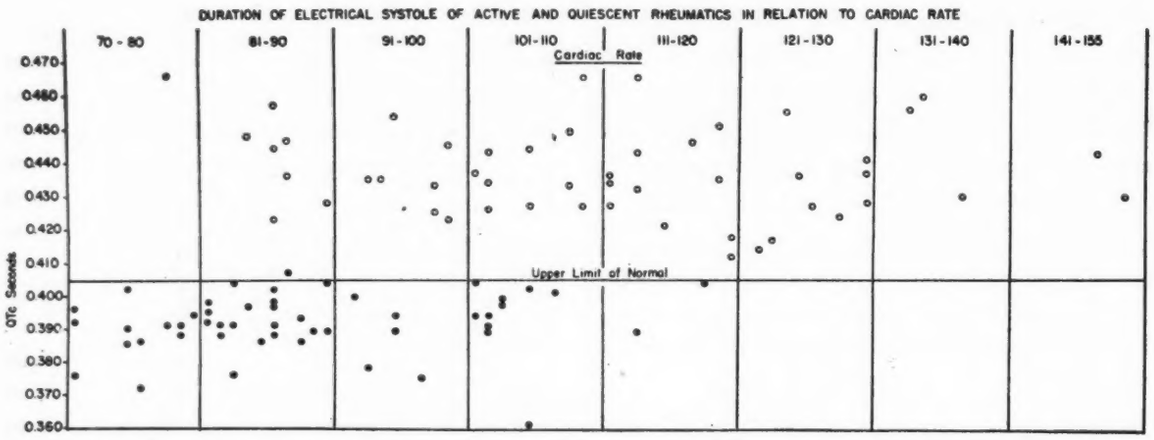

FIG. 3. Duration of electrical systole in children with active and quiescent rheumatic fever in relation to cardiac rate. On this chart, fifty "active" and fifty "inactive" cases are distributed according to the Q-Tc of the patients at the time of the observation and the cardiac rate at the same time. (Courtesy of *Am. Heart J.*, 33: 14–26, 1947.)

for many years measured the electrical systole in children having rheumatic carditis. Since the electrical and mechanical systoles, for clinical purposes, are equivalent, a disturbance in the relationship between systole and diastole would show up in the measurement of the electrical events in the cardiac cycle. Our studies show that:[20]

1. "The duration of the electrical systole (Q-T) both absolute and relati ve to diastole is significantly prolonged in all cases of acute carditis. (Fig. 3.)

2. "This prolongation does not seem to be a function of cardiac rate in these cases but rather that of the severity of the disease."

3. While it cannot be said that the prolongation of the electrical systole signifies an acute inflammatory process in the heart muscle, our studies show that all cases of acute carditis present such a disturbance in the electrical sequence of events of the cardiac cycle.

For the present we are satisfied with the observation that prolongation of the electrical systole in the cardiograms of children suffering from rheumatic carditis is an important diagnostic criterion of the presence and degree of rheumatic activity in the heart muscle. There is evidence to show that this finding precedes all other laboratory criteria of rheumatic activity and does not return to normal for long periods of time after all other criteria have reached a normal level.

SUMMARY OF LABORATORY CRITERIA

In summary then, those laboratory and clinical measurements upon which considerable reliance is placed in evaluating the progress of rheumatic disease do not seem to be adequate for a diagnosis of rheumatic activity. At the end of nine months after the onset of rheumatic activity all children in our group showed normal white blood counts, hemoglobin, sedimentation rate, vital capacity and pulse rates. At this time, a large percentage continued clinically to demonstrate rheumatic activity. While it is true that some of the laboratory tests remain abnormal for a longer period of time than others, none of those currently used is adequate in screening all cases of active rheumatic disease. In our experience, a study of the electrical events in the cardiac cycle seems, for the present, to be the most sensitive method of detecting the presence of rheumatic activity.

DISCUSSION

QUESTION: On what basis can we make a diagnosis of rheumatic disease in a patient

who has definite evidence of mitral stenosis but does not present a definite history of rheumatic fever or rheumatic symptoms? The current teaching seems to be that the etiological diagnosis of rheumatic disease cannot be made unless there is a definite history.

DR. TARAN: Mitral stenosis should always be set down as rheumatic in origin unless another etiologic basis is known. It might be said, however, that in our experience no case of mitral stenosis was observed without a history of rheumatic disease. It must be admitted that these histories are often very difficult to obtain.

QUESTION: There are some studies in the literature which seem to postulate that chorea is not a manifestation of rheumatic fever. How do you explain such conclusions?

DR. TARAN: In the light of our present knowledge such conclusions cannot be accepted. In the first place, most cases of chorea have other manifestations of rheumatic disease. In the second place, careful follow-up of chorea patients over long periods of time show an incidence of classical rheumatic heart disease much higher than one would expect in any normal group of individuals.

QUESTION: Not infrequently one sees in private or clinic practice children with a known history of rheumatic disease who present no rheumatic manifestations or symptoms but who have a slight elevation in temperature daily for many weeks or months. No explanation for this fever can be discovered on physical examination. How are we to interpret this low-grade fever?

DR. TARAN: It is common experience that some very active children normally have a temperature above the so-called normal, particularly following vigorous physical activity. A temperature slightly above 100°F. (37.8°C.) is not infrequently registered in this group of children late in the afternoon. A short rest lowers the temperature level to "normal." In our experience, such individuals are found among rheumatic children with the same frequency as among normal groups of children. It is noteworthy that the daily fluctuation of temperature in this group is not measurably greater than the average for any group of children.

Occasionally, a child recovering from an acute rheumatic episode continues to have a slightly elevated temperature for many weeks while at rest. Our observations seem to show that this isolated clinical finding cannot be considered significant of rheumatic activity. More often than not, such patients show a normal temperature level when they are returned to normal physical activities.

QUESTION: How much reliance can one place upon the finding of a rapid pulse rate in a child?

DR. TARAN: The sleeping pulse rate is a good index of the actual cardiac rate as it excludes the hurried heart rate resulting from the inimical doctor-patient relationship. It should be remembered, however, that many children go through their day's experiences during sleep. This may produce a hurried cardiac rate during sleep. In most children, in our experience, a carefully studied approach to the child will avoid all apprehension and the cardiac rate observed under these circumstances can be relied upon as representing the actual rate.

QUESTION: Not infrequently one sees a child with rheumatic disease who after several weeks of bed rest does no longer present any rheumatic manifestations except an elevated sedimentation rate. Would you allow such a patient to assume normal activities gradually?

DR. TARAN: Yes, if I were reasonably assured that this patient no longer presents clinical evidence of rheumatic activity. In our experience, the elevated sedimentation rate in such a patient is not significant of rheumatic activity. If no other explanation

for the elevated sedimentation rate can be found, the patient should be observed but not stigmatized as having active rheumatic disease on the basis of this finding alone.

QUESTION: You state that the prolongation of the electrical systole (Q-T) is characteristic of acute carditis and is a valuable method for evaluating the severity of carditis. What is the physiologic significance of this finding? Little mention is made of the clinical significance of the Q-T interval in most texts on cardiography. Is there any explanation for this omission?

DR. TARAN: Physiologists have always contended that disturbance in the time relationship of systole and diastole is a manifestation of impairment of the functional integrity of the myocardium. They found consistently that the period of systole was of longer duration in functional cardiac disorders. When more than normal blood returns to the ventricle, it responds by expelling more blood not only by a greater number of ejection periods but also by a greater relative duration of each systole. To the physiologist the duration of systole in a diseased heart as compared with the normal heart gives a method of determining the functional integrity of the myocardium; and some physiologists state that the duration of systole in the abnormal heart is a measure of dilatation.

There is, however, a wide difference of opinion among cardiographers and clinicians regarding the clinical importance of the measurement of the duration of the electrical systole (Q-T). Katz[21] states that "there is little practical value in measuring the duration of electrical systole." Ashman,[22] on the other hand, believes that measurement of the electrical systole may give valuable information regarding the degree to which the myocardium is affected in diphtheria or in acute rheumatic carditis. Cheer[23] presented evidence to show that the electrical systole (Q-T) is greatly increased in heart failure irrespective of etiology and proposed the concept that an increased electrical systole may indicate a disturbance of cardiodynamics which might well be formed before clinical evidence of failure is available. Drawe[24] and his associates find that the Q-T interval is definitely prolonged in about 25 per cent of the rheumatic children he observed. On the other hand, White and Mudd[25] conclude that the duration of the Q-T interval is apparently of little or no clinical value.

It is clear that while physiologists are in agreement that prolongation of the duration of systole (Q-T) is significant of a disturbance in the functional integrity of the myocardium, clinically insufficient evidence has been forthcoming in support of the physiologic concept. This discordance of opinion may be explained on the basis that the study of the component parts of the cardiac cycle have not been closely investigated in hearts showing acute impairment of myocardial function such as rheumatic carditis but rather in cardiac conditions of long-standing in which functional compensation has already been established at a given level of cardiac reserve.

SUMMARY OF SEMINAR

The clinical manifestations and laboratory criteria of rheumatic activity have been the subject for discussion in this seminar. It has been pointed out that rheumatic disease in children is a long-standing systemic disease presenting systemic and localized clinical manifestations. It has also been pointed out that while the number of clinical manifestations are many and varied, the dominant feature of the disease is protracted, long-enduring activity manifested mainly in disturbance in the cardiovascular system. It has further been pointed out that emphasis should be directed toward the diagnosis of *mild* rheumatic activity. More attention is to be given to the patient and

his heart. It is believed that all cases of rheumatic activity demonstrate clinically cardiac auscultatory findings significant of disturbance in the functional integrity of the heart.

It has further been pointed out that all the laboratory tests currently used in the diagnosis of rheumatic activity are inadequate in screening rheumatic activity. The most sensitive criterion for rheumatic activity for the present seems to be a careful study of the cardiac events in the electrocardiogram. Observations seem to show that rheumatic activity continues for long periods of time after temperature, pulse rate, white blood count, sedimentation rate, hemoglobin and vital capacity have returned to normal. The disturbance in the sequence of events in the cardiac cycle, however, is the last criterion to return to normal and, in our experience, seems to coincide as closely as possible with the cessation of rheumatic activity.

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Combined Staff Clinics

The Nephrotic Syndrome

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. ROBERT F. LOEB: Dr. Coleman is going to summarize the story of a girl who was in this hospital one year ago and at that time presented the classical picture of the nephrotic syndrome.

DR. THOMAS COLEMAN: This is E. L., now twenty-one. The story of her disease begins three years ago when, in July, 1943, at the age of eighteen, she first began to notice intermittent ankle edema. The edema increased and she consulted a doctor. He found a 4 plus albuminuria. Her weight at that time was 148 pounds. Her doctor put her on a low-salt, low-protein diet, on which she stayed rather regularly for one year. During the last three months of that year she began to lose weight rather markedly, became very pale, had anorexia, severe nausea and vomiting. When she reached the weight of 113 pounds she decided voluntarily to break the diet and began eating anything she liked, including salt. She then gained weight for one year despite treatment with diuretics by a second physician. Her weight had increased to 158 pounds at the time of her first Presbyterian Hospital admission in July, 1945. She had never had any acute upper respiratory or other infection. Characteristic symptoms of acute glomerulonephritis could not be elicited in her history. She had no exposure to nephrotoxins such as carbon tetrachloride. There was no history of hypertension. In short, her past history was noncontributory.

On physical examination at admission she showed massive edema, ascites, bilateral hydrothorax, pallor. The blood pressure was normal. Her thyroid was enlarged. The initial tests showed an antistreptolysin titer of less than 50. The phenolsulfonphthalein excretion was 50 per cent after two hours. The Kline test was negative. Nose and throat culture was negative for hemolytic streptococcus and pneumococcus. The basal metabolic rate was minus 20 per cent. Fasting blood sugar was normal.

Her treatment consisted of diet low in sodium and high in protein. She was given diuretics including urea, mercurials and ammonium chloride. She was placed, for a time, on the Schemm regimen, which is essentially sodium-free but includes a high water intake.

Despite these therapeutic measures she failed to improve. In fact, she gained weight, which was presumably edema fluid. Her weight remained above 160 pounds. Her red blood cell count fell from five million to three million per c. mm.; the hemoglobin from 14 to 12 Gm. per cent; the total serum protein ranged between 3.6 and 2.5 Gm. per cent. Her serum albumin fell on one occasion to as low as 0.8 Gm. per cent. The blood urea nitrogen ranged around 25 mg. per 100 cc., exclusive of a period of urea therapy, at which time it rose. Her cholesterol on admission was 895 mg. per cent, and at one time reached a high of 1,560 mg. per cent; on discharge it was 1,100 mg. per

cent. Her urine during all this time continued to show 4 plus albumin, 2 plus glucose, with many hyaline and granular casts and an occasional red blood cell. After ten weeks without much success in treatment she was discharged to be followed in the out-patient clinic.

She was seen in the clinic at regular intervals for eleven months, during which period she did no work and remained at home. She maintained a rigid salt-poor regimen with a moderate protein intake sufficient to maintain nitrogen balance. The serum albumin rose to 3 Gm. per cent, the serum cholesterol fell from 1,400 to 460 mg. per cent. She lost weight, dropping from 148 to 125 pounds in six months. However, toward the end of her clinical follow-up, the serum non-protein nitrogen began to rise, increasing from 44 to 155 mg. per cent. The hemoglobin fell from 12 to 5 Gm. with a corresponding decrease in red cells. Her appetite was poor. She began to have nocturnal muscle cramps and great fatigue. Phenolsulfonphthalein excretion fell to zero. Heavy albuminuria continued, with normal blood pressure. She was then admitted for the second time in October, 1946, for treatment of her anemia.

On admission she weighed 120 pounds and was free of edema. She was given a low-protein, low-sodium diet. She received 1,400 cc. of whole blood and her hemoglobin rose to 8 Gm., the red blood cell count to four million. Despite fluid therapy, her blood urea nitrogen increased during this admission to 130 mg. per cent. Recently, she has shown the first rise in blood pressure, which in the last two weeks has been ranging about 140 to 160 systolic and 110 to 120 diastolic. Her albuminuria continues 4 plus, with casts. She is being discharged today showing marked subjective improvement despite progressive renal failure. The only objective change for the better has been an increase in hemoglobin following

TABLE I

PATIENT E. L., NEPHROTIC SYNDROME

Date	Edema	Albuminuria	Blood Pressure, Mm. Hg.	Hemoglobin, Gm.	Total Serum Protein, Gm. Per Cent	Serum Cholesterol, Mg. Per Cent	Serum N.P.N., Mg. Per Cent	Serum Urea Nitrogen, Mg. Per Cent
June 1943	++	++++						
December 1943	0	++++						
July 1944	++	++++						
July 1945	+++	++++	132/87	14.5	3.6	895		21
August 1945	++++	++++	135/96	15.4	2.9	1561		54
September 1945	+++	+++	128/100	14.0	2.5	1379		29
November 1945	++	+++	120/95		4.1	1479	44	
January 1946	++	++++	120/80		6.1	1308	61	
April 1946	+	++++	125/90		3.8	1119	67	
September 1946	0	++++	125/90	4.6	5.4	459	153	
Oct. 5, 1946	0	++++	146/88	4.0	5.5	485		107
Oct. 11, 1946	0	++++		5.0*				62
Oct. 17, 1946	0	++++		6.5†				77
Oct. 23, 1946	0	++++	144/110	7.0‡	5.0	378		97
Nov. 18, 1946	0	++++	190/135	8.0				145
Nov. 22, 1946				7.5				170

* After one transfusion (150 cc. whole blood).
† After two transfusions (450 cc. whole blood).
‡ After four transfusions (1450 cc. whole blood).

repeated transfusions. The laboratory data on this patient are summarized in Table 1.

DR. LOEB: What has transpired in this girl is compatible with the natural history of the nephrotic syndrome and probably bears little relationship to the therapeutic measures employed.

I think perhaps it would be just as well to begin our discussion with the origin of the term "nephrosis," which was coined in 1905 by Friedrich Müller. He applied this name to *degenerative* lesions of the kidney primarily involving the tubules, and used it to differentiate these lesions from *inflammatory* lesions of the kidney. We are concerned today with what has come to be known as the "nephrotic syndrome" and not with all states characterized by tubular degeneration.

As all of you know, the nephrotic syndrome is characterized by heavy albuminuria, edema, hypoalbuminemia, in most instances hypercholesterolemia, and in some instances a lowering of the basal metabolic rate. The nephrotic syndrome is encountered characteristically and most frequently in chronic glomerulonephritis. It is also seen, as you know, in the so-called true or lipoid nephrosis. It has been described recently by McCann in Leptospira infection. As suspected for a long time, it may occur in secondary syphilis; dramatic cures with penicillin have definitely established this etiology in a few cases. The nephrotic syndrome is encountered also in the so-called Kimmelstiel-Wilson syndrome. It is also seen in amyloidosis and, of course, at times following poisoning with certain chemical agents, notably carbon tetrachloride. So you see the development of the nephrotic syndrome is not limited to purely degenerative disease of the kidneys, as indicated by Müller originally, but it is associated with both inflammatory and degenerative disorders.

The problem of the relationship of tubular degenerative lesions to the nephrotic syndrome is both of interest and importance. It should be pointed out in the first place that there are many patients who show marked degenerative lesions in the tubules who do not manifest the nephrotic syndrome. Next, I think it is important to remember that a certain amount of protein traverses the glomerular membrane normally and this is mostly reabsorbed by the tubule cells. It would be generally conceded today that, in the nephrotic state, proteinuria results from glomerular rather than tubular changes. Serum protein appears in the glomerular filtrate either as a result of increased porosity of the glomerular capillaries or because of some change in the electrostatic charges of the capillary membrane. Possibly changes in charges of the protein aggregates themselves may play a part; this is purely speculative.

Another point important to remember is that the tubular lesions which develop in the nephrotic state are probably in many instances secondary to the albuminuria, and are not primary as was originally believed. The evidence for that is threefold. First, we know that biopsy of a kidney in a patient who has recently developed the nephrotic syndrome may show no histological deviation from the normal structure of the tubular epithelium, whereas later biopsy of the same kidney reveals the typical tubular changes. Second, Gérard in classical experiments on the salamander found that injection of plasma into the peritoneal cavity was associated with development of tubular degeneration in those nephrons connected with the nephrostomes in the peritoneal cavity, whereas the remaining tubules were normal. Finally, Smetana, here at Columbia, extended Gérard's observations and demonstrated graphically that albumin was reabsorbed in large amounts from the tubules with peritoneal nephrostomes when a red azo-protein was

injected intraperitoneally in the salamander. The cells of the tubules communicating with the nephrostomes were loaded with this pink material whereas none of the other tubules contained the protein dye.

As far as the *mechanism of the nephrotic syndrome* is concerned, I think the historical background is of some interest. In 1916 and 1917, Epstein first pointed out what seemed a logical thesis for the mechanism of the nephrotic syndrome. Epstein indicated that with the heavy albuminuria which is present in these patients there is continued loss of serum albumin and some globulin through the kidneys. This in turn he believed gives rise to hypoalbuminemia. Epstein was the first to apply the Starling hypothesis to the formation of edema. He pointed out that if a large amount of serum albumin is lost, the most important osmotic component of the blood is reduced and consequently the development of massive interstitial edema might be anticipated. Epstein further reasoned that if a large amount of serum albumin is lost through the kidneys, the conventional treatment of nephritis by protein starvation was illogical and he suggested that an increased protein intake might restore the serum albumin to its normal level. Experience of the last thirty years has demonstrated that this thesis is not wholly valid. It is general experience that when patients with the nephrotic syndrome are fed massive amounts of protein, positive nitrogen balance may be established and body protein stored; but evidence that a significant increase in serum albumin level is brought about by this treatment is wanting. We now think that the metabolic disturbances in the nephrotic syndrome are probably much more widespread and profound than was appreciated earlier, and that simple leakage of albumin through the kidneys is not alone an adequate explanation for the abnormalities encountered. It has been suggested by Kendall, Grabfield, Luetscher and others that there appear to be qualitative as well as quantitative changes in the serum protein in the nephrotic state. I am going to ask Dr. Kendall, who has done important work in this field, to talk about his studies on serum proteins in the nephrotic state.

Dr. Forrest E. Kendall: Dr. Loeb asked me to spend about five minutes in telling you what I know about serum proteins in nephrosis. I will not try to discuss any of the technics which have been used in the study of serum proteins. There are many. They include the salt precipitation methods, as exemplified by the Howe procedure; precipitation with alcohol or other organic solvents under controlled conditions, as exemplified by the work of Cohn and his associates; electrophoresis, ultracentrifugal studies, amino acid analyses, quantitative precipitin studies and many more. These investigations all show that blood serum contains an extremely complicated mixture of proteins varying in molecular weight from around 70,000 to several millions. It contains proteins which would be classified as simple proteins and proteins which are associated with carbohydrates and with lipids.

During the past year in this room, in response to a direct question, Dr. Pedersen of Upsala said that he would hesitate to place any upper limit on the number of protein components in normal human serum. But he felt sure that the number would exceed twenty. In view of this, it is apparent that no technic at present available and no combination of technics will give a complete picture of the serum proteins, even in healthy individuals. But we should not allow this fact to make us disregard the value of serum protein studies in connection with disease. It should simply make us more confident that these studies will become increasingly valuable as our knowledge of the serum proteins increases.

It is interesting that from a clinical standpoint the crudest and simplest of the methods for the study of serum proteins is the most important. That is the Howe fractionation procedure, which really tells us very little of the actual chemistry of serum proteins. However, a large amount of data has been accumulated using this technic and it is possible to make certain correlations between the results of the Howe fractionation and some clinical disorders. From a practical standpoint, the Howe method is today and will probably continue for a long time to be the most valuable tool in this field.

Inasmuch as nephrosis, as defined by Dr. Loeb, is characterized by hypoalbuminemia, we will certainly have to say that the level of serum albumin as determined by the Howe method decreases in the nephrotic syndrome, sometimes to extreme degrees. The serum globulins as determined by the Howe procedure usually remain within normal limits. In my experience, serum globulin levels in nephrosis were below those found normally only in patients in whom there was evidence of blood dilution in addition to nephrosis.

The protein excreted in the urine is largely albumin. I place little reliance upon the results of Howe fractionations as applied to the proteins of urine.

What additional information has been obtained by the use of other technics in this condition? As you know, it can be shown by the use of the Tiselius electrophoresis technic that the normal serum proteins can be separated on the basis of their electrical mobilities into four fractions. The fastest moving fraction has been identified as serum albumin. The other three fractions are considered to be globulins, designated alpha, beta and gamma globulins in the order of decreasing mobility and are found in approximately equal amounts in normal serum. If electrophoretic studies are made upon the albumin fraction obtained in the Howe procedure, it can be shown that it contains some globulin; therefore, values obtained for serum albumin in normal individuals are somewhat lower than those given by the Howe method.

Refinements of technic have shown that these different electrophoretic fractions can be further subdivided. Thus the albumin fraction, when measured at a pH below 4, can be split into two components with approximately two-thirds of the albumin moving in the faster fraction.

In nephrosis or in the nephrotic syndrome, electrophoretic studies show even greater decreases in the albumin level than are found by the Howe technic. Most of the decrease in the albumin occurs in the faster moving fraction. In the globulins, there is usually an increase in alpha globulin and a corresponding decrease in gamma globulin. Table II, taken from a paper by Thorn and his co-workers, shows the distribution of components in electrophoretic schlieren diagrams (pH 8.6 with sodium diethylbarbiturate as buffer) of plasma proteins in the nephrotic syndrome. In patients with the nephrotic syndrome, quantitative measurements are complicated by the presence of large amounts of lipid moving with the alpha and beta components. Estimations of these fractions are subject to very large positive errors due to the high refractive index of the lipid components.

The protein in the urine is largely albumin and most of this albumin is the faster moving fraction. A large part of the globulin in the urine is gamma globulin.

Immunological studies show very much the same picture. By this technic it can be shown that there are at least five distinct globulins and two albumins in normal serum. It can be shown that approximately two-thirds of the albumin is the carbohydrate-free albumin which can be crystallized. I cannot state that this is the albumin

fraction which moves at a faster rate in the electrophoretic cell. I can say that most of the albumin that is excreted in the urine is the crystalline albumin. The serum globulins show the same shift from gamma globulin to alpha globulin which is indicated by electrophoretic technics.

In conclusion, I should say that the characteristic changes in the nephrotic syndrome are decreases in the blood level of those serum proteins which are excreted in the urine, plus an increase in the alpha globulin fraction.

DOCTOR: Is there any evidence that abnormal proteins occur in the serum of patients with the nephrotic syndrome?

DR. KENDALL: I know of no conclusive evidence that nephrotic serum contains proteins not present in the serum of normal individuals. Various investigators have shown that the albumin and globulin fractions of nephrotic serum may differ from corresponding fractions prepared from normal serum in their amino acid content, in osmotic pressure and in their reaction with antisera. However, one must remember that this work was done upon fractions of serum rather than upon pure proteins. It seems to me that it is more probable that the results are due to changes in the relative proportions of normally occurring albumins and alpha globulins in the fractions than to the appearance of new proteins.

DR. LOEB: In addition to the changes which occur in the serum proteins in the nephrotic state, edema, as we have said already, is a characteristic feature of this disorder. Edema fluid is essentially a solution of sodium chloride and sodium bicarbonate with variable amounts of protein. It was shown originally by Blum and simultaneously by Magnus-Levy that if sodium salts such as chloride or bicarbonate are administered to patients with the nephrotic syndrome, there is an increase in water retention. This increase is found in the interstitial fluid; the plasma volume in patients with the nephrotic state is in reality lower than in normal individuals. Furthermore, Blum and Magnus-Levy showed that it is the sodium ion (and not the chloride and bicarbonate ions) which is active in the production of edema because the administration of potassium, ammonium or calcium chloride tends to have a diuretic effect and to decrease water retention. In

TABLE II*

DISTRIBUTION OF COMPONENTS IN ELECTROPHORETIC SCHLIEREN DIAGRAMS† OF PLASMA PROTEINS IN THE NEPHROTIC SYNDROME

Patient	Albumins	α_1 Globulins	α_2 Globulins	β Globulins	Fibrinogen	γ Globulins
	(Per Cent)		(Per Cent)		(Per Cent)	
J. G.	7	4	42	28	16	3
L. I.	17	5	36	22	16	4
W. H.	17	5	21	38	15	4
D. S.	26	8	22	30	9	5
K. N.	37	6	15	22	12	8
E. B.	46	4	34‡		13	3
R. S.	32	5	20	23	(clotted)	20
Normal pooled human plasma	55	5	9	13	7	11

* Adapted from G. W. Thorn, S. H. Armstrong, Jr., V. D. Davenport, L. M. Woodruff and F. H. Tyler. *J. Clin. Investigation*, 24: 802, 1945.

† Sodium diethylbarbiturate buffer, pH 8.6.

‡ Not resolved.

view of these differences in specific ion effect on water retention and excretion, the mechanism of renal control of electrolyte equilibrium is, in addition to the osmotic factor, of unquestionable significance in edema production.

Dr. Taggart will discuss briefly sodium and water metabolism in relation to the kidney in the nephrotic syndrome.

DR. JOHN V. TAGGART: Since the clinical problems posed by the nephrotic patient arise primarily from disturbances of salt and water balance, it is fitting that we consider briefly the mechanisms which may be involved in the formation of edema in nephrosis.

The low protein concentration of edema fluid in nephrosis speaks against increased capillary permeability as an important factor. The various diffusible ions are distributed between the plasma and edema fluid in accordance with the Donnan equilibrium. It has been clearly demonstrated that serum and edema fluid obtained from a nephrotic individual retain their original ionic constitutions when separated by a simple collodion membrane. In short, the edema fluid of nephrosis may be regarded as an ultrafiltrate of plasma subject to the ionic balance imposed by the nondiffusible plasma proteins.

It has long been recognized that the scanty urine excreted during the accumulation of edema contains unusually small amounts of salt. Widal, Javal and other investigators at the turn of the century were much impressed by the systematic variations in the amount of edema which could be induced by varying the salt intake in their patients. Such observations led to the belief that the accumulation of edema reflects a specific renal defect in the excretion of sodium chloride. An obligatory retention of water occurs in order that the all-important osmotic equilibria may be maintained.

In recent years plasma clearance studies with inulin, diodrast and *p*-aminohippuric acid have made possible the description of certain discrete renal processes in health and disease. The nephrotic syndrome in chronic glomerulonephritis occurs in the presence of a renal lesion which usually disturbs the normal relationship between the glomerular filtration rate and the functioning tubular mass. Characteristically there is a preponderant diminution of the glomerular filtration rate in glomerulonephritis. This finding suggests that sodium retention may be the consequence of an imbalance between the capacity of the kidney to filter and reabsorb sodium ions. It should be remembered that the total amounts of sodium and water filtered and reabsorbed daily by the normal kidneys are approximately 500 Gm. and 180 liters, respectively, and that relatively minor disturbances of the normal balance could readily account for the sodium and water retention occurring in nephrosis. The functional pattern in so-called true lipoid nephrosis appears to be different from that of glomerulonephritis. Limited observations indicate that the glomerular filtration rate, effective renal plasma flow and functioning tubular mass all tend to have supernormal values. The large kidney of lipoid nephrosis is a large, functioning kidney. This situation, however, does not exclude the possibility of internal imbalances between glomerular filtration and tubular reabsorption.

While the functioning tubular mass, as measured by diodrast or *p*-aminohippuric acid, may give some indication of the activity of the tubular transfer mechanism for sodium, one can say little at this time concerning the nature of the sodium reabsorptive mechanism. Not until such information is available will one be able to assign to the kidney its proper rôle in the formation of edema in nephrosis.

The development of the Starling concept shifted emphasis from a specific renal defect to the rôle of hypoproteinemia in edema formation. The balance between the colloid osmotic pressure of plasma and the hydrostatic pressures in the arterial and venous limbs of the capillaries might well be expected to be disturbed by the lowering of plasma albumin characteristic of nephrosis. The development of this concept in relation to nephrosis was advanced most notably by the studies of Epstein and Leiter. Epstein examined the relationship between plasma protein concentrations and edema formation in nephrotic patients, while Leiter's studies were concerned with the induction of hypoproteinemia by repeated plasmapheresis in dogs. It was their conclusion that the lowering of plasma protein concentrations below certain critical values was almost invariably associated with edema collection and that hypoproteinemia alone offers an adequate mechanism for edema formation. However, in subsequent years there have been all too numerous instances in which investigators have observed the mobilization and excretion of edema fluid without demonstrable changes either in the plasma protein concentration or the colloid osmotic pressure. Thus, hypoproteinemia alone does not appear to offer an adequate basis for explaining the formation and maintenance of edema in nephrosis.

Let us return then to considerations of a specific renal defect in the handling of sodium ions. Loeb, Atchley and their coworkers examined the water and electrolyte balance in nephrotic and normal individuals following the administration of sodium chloride and various other electrolytes. While the responses obtained in the two groups of subjects were qualitatively similar, there were quantitative differences which these investigators considered to be of importance.

Dr. Loeb: As Dr. Taggart has pointed out to you, there is another serious defect in the simple hypothesis of Epstein concerning the mechanism of the nephrotic state, namely, that many patients may achieve complete diuresis spontaneously without any rise whatsoever in the serum albumin level. Spontaneous and complete diuresis may be effected despite levels of only about 1.5 Gm. of serum albumin per 100 cc. This fact suggests that nephrotic edema is not solely a consequence of hypoalbuminemia, although the importance of depression of the serum osmotic pressure should not be minimized, as indicated by the studies of Govaerts and others.

Dr. Peters and also Dr. Van Slyke established what they termed a "critical level" of serum albumin for fluid retention in the body. I think, however, that Dr. Taggart's comments emphasize the fact that these so-called "critical levels" for edema formation are not inviolate. Furthermore, as pointed out by Govaerts, patients with famine edema and marked decrease in serum osmotic pressure have a large diuresis when they assume the horizontal position, i.e., when the hydrostatic pressure is lowered. In the nephrotic patient with even more generalized edema and low serum osmotic pressure, diuresis is not similarly effected by bed rest.

Another indication that mechanisms other than the osmotic factor may be involved in excessive salt and water retention is suggested by the effects of certain steroids, notably desoxycorticosterone. With low serum albumin levels the latter steroid may cause extraordinary increases in the interstitial fluid compartment and massive anasarca may result. At the present time, we ascribe this increased reabsorption of water and of sodium ion to the effect of the steroid upon specific tubular function. Other steroids such as testosterone and some of the estrogens may cause salt and water

retention but to a lesser degree than does desoxycorticosterone.

Another factor possibly involved in the production of the nephrotic state as characterized by massive edema may be the excessive elaboration or decreased degradation of antidiuretic substances. I have asked Dr. Gilman, who I think was the first to demonstrate the presence of antidiuretic substances in the urine of normal but dehydrated rats, to talk about the possible rôle of antidiuretic substances in the development of the nephrotic state.

DR. ALFRED GILMAN: During recent years attention has been focused on derangements in mechanisms of water excretion to account for the accumulation of edema fluid observed during certain clinical syndromes. Many of the observations are pertinent to the present discussion. I would, therefore, like to review very briefly the physiological mechanism of water excretion.

If large amounts of water are ingested, a copious urine flow results. The urine has a very low specific gravity and is practically devoid of electrolyte. This is accomplished by tubular renal mechanisms whereby the reabsorption of water is depressed whereas that of electrolyte is practically complete. This is a rather intricate function which involves osmotic work on the part of the kidney for it should be recalled that the expenditure of energy in the elaboration of a hypotonic urine is just as great as in the elaboration of a hypertonic urine. Thus it is rather paradoxical to find that the ability of the kidney to excrete a hypotonic urine depends not on the presence but rather on the absence of a particular hormone, namely, the antidiuretic hormone of the posterior pituitary gland.

Our present concept of the mechanism by which the renal excretion of water is accomplished is as follows: The degree of cellular hydration is interpreted by sensitive centers in the hypothalamus. These have a direct connection by means of the hypothalamic pituitary tract with the secreting cells of the posterior pituitary. Dehydration increases the secretory activity of the posterior pituitary; hydration decreases secretory activity. With secretory activity stopped, the circulating antidiuretic hormone is rapidly destroyed and water diuresis results. A finding pertinent to our discussion is the fact that small amounts of antidiuretic hormone escape into the urine and apparently reflect the blood concentration. Thus in hydrated experimental animals and humans no antidiuretic hormone can be detected in the urine, whereas in dehydrated subjects in whom the need for water conservation is great, the urine contains a huge concentration of an antidiuretic substance.

That derangements should occur in such a sensitive system is not at all surprising. The disturbances in water metabolism which accompany posterior pituitary insufficiency are well known in connection with the large daily urine volumes which are characteristic of diabetes insipidus. The possibility that there may be an antithetical syndrome has been largely ignored. Theoretically an abnormally high concentration of antidiuretic substance in the blood could result from (1) an excessive secretion of the posterior pituitary, (2) a failure of the mechanism whereby the antidiuretic substance in the circulation is destroyed in order to permit the excretion of water, or (3) the formation in some other tissue of an antidiuretic substance. In the event that excessive amounts of water are reabsorbed by the kidney, the subsequent reabsorption of electrolyte for the purpose of maintaining osmotic homeostasis would be in order. The result would be a plethora of extracellular fluid.

The possibility that the accumulation of extracellular fluid may be the result of inadequate renal excretion of water has been investigated in three types of disorders;

the ascites of hepatic cirrhosis, the edema of eclampsia and the edema of nephrosis.

Ralli and her associates could find no casual relationship between the formation of ascitic fluid and the concentration of plasma protein in patients with hepatic cirrhosis. However, those patients who were forming ascitic fluid rapidly exhibited a high concentration of an antidiuretic substance in the urine. Conversely, no antidiuretic substance could be detected in the urine of those patients in whom ascitic fluid was not accumulating. They suggest among other possible explanations that hepatic cirrhosis may interfere with the normal destruction of antidiuretic hormone.

A number of investigators have tested the urine of eclamptic individuals for antidiuretic substances. All observations are in essential agreement and I will only cite those of Ham and Landis. They observed that the urine of eclamptics contained significant amounts of an antidiuretic substance which could not be detected in the urine of women experiencing a normal pregnancy. Differences in the characteristics of the antidiuretic substance obtained from the urine and that obtained from pituitary gland prompted Ham and Landis to examine the placentas. They found an antidiuretic substance in the placentas of eclamptic patients in contrast to those obtained from individuals at the termination of an uncomplicated pregnancy.

Finally, Robinson and Farr have examined the urine of nephrotic individuals. In the same patients the urine contained an antidiuretic substance during periods of formation of edema fluid but not during periods of mobilization of edema fluid. They could make no correlation, however, with the direction of fluid movement and the concentration of plasma protein.

This briefly is the status of the possible rôle of antidiuretic substances in the etiology of edema. Obviously the burden of proof rests with those who champion such a mechanism. However, provocative evidence is already at hand to suggest a primary rôle of the kidney in edema formation.

DR. HENRY ARANOW, JR.: As I remember, Ham and Landis differentiated between their placental antidiuretic substance and the posterior pituitary antidiuretic substance on the basis of chloride excretion. Is this difference in chloride excretion also found in the dry and wet stages of the nephrotic syndrome?

DR. GILMAN: There is a difference of opinion as to the effect of the posterior pituitary hormone on the excretion of chloride. Peters is of the opinion that it has very little effect on the excretion of electrolyte.

Robinson and Farr made no attempt to characterize their antidiuretic substance. They just accepted the fact that it was antidiuretic. As I recall, no studies were made of chloride excretion in their patients. Ralli and her group tried to characterize the substance they found in their cirrhotic patients and as far as they could tell on the basis of chloride excretion, it was identical with the posterior pituitary antidiuretic substance in that it had no effect on the urinary excretion of chloride. Also, they could easily eliminate the effect on chloride excretion of the posterior pituitary by dialysis.

DOCTOR: Since the plasma proteins tend to be low in the nephrotic syndrome, I was wondering whether this acts as a stimulus to production of antidiuretic hormone.

DR. GILMAN: I do not think anyone has made the implication that the production of antidiuretic hormone is necessarily increased in the nephrotic syndrome. We may merely have an altered balance between destruction and production.

STUDENT: If water retention is the result of increased level of antidiuretic substance,

why should just limitation of the sodium intake affect the amount of edema fluid?

DR. LOEB: I would say there that restriction of sodium is not nearly as dramatic as the administration of sodium in the opposite direction.

DR. DAVID SEEGAL: I should like to ask Dr. Gilman if Landis and Ham's work has been confirmed?

DR. GILMAN: There have been four or five studies on the excretion of antidiuretic substances during eclampsia. The authors have tried to relate increased concentrations of posterior pituitary substance to hypertension and edema. There appears to be some relation to edema but not to hypertension. In this respect the observations of Ham and Landis are in agreement with others. However, I do not believe anyone else has attempted to confirm the placental origin of the antidiuretic substance.

DR. LOEB: As additional evidence of a further widespread disturbance in the nephrotic state, I think we can re-emphasize the fact that serum albumin does not increase with high protein feeding as it does in nutritional edema following the administration of a high protein diet. Indeed, it is believed by many that there is a failure of the normal elaboration of serum albumin in these patients. Furthermore, as already pointed out, hypercholesterolemia is a typical finding in patients with the nephrotic state; the reason for this abnormality has not been clarified. Also, as we have said, nephrotic patients very often have a sharp depression of the basal metabolic rate, which cannot be correlated with any demonstrable change in the thyroid gland, and the reason for which is obscure. It cannot be stated at this time whether these changes in the nephrotic state are primary or secondary to the prolonged hypoalbuminemia. I think we can end the discussion concerning possible factors relating to the mechanism of the disease at this point and turn our attention to the more clinical aspects of the syndrome.

It must be stated at the outset that the *course and duration* of the nephrotic syndrome are to a great extent dependent upon the precipitating cause. Thus, syphilitic nephrosis is terminated promptly by the administration of penicillin. The carbon tetrachloride nephroses end either favorably or unfavorably in a short period of time. The course of "true" or "lipoid" nephrosis and of the nephrotic state of glomerulonephritis is extraordinarily variable and unpredictable.

Patients with the nephrotic stage of chronic glomerulonephritis complain only of the mechanical discomfiture resulting from massive edema and perhaps of some fatigue. On the disappearance of edema, the nephritic patient is usually elated and feels at long last that all is well. Unfortunately, in the majority of instances, the loss of edema presages advance of the disease, as illustrated by the girl you saw today. She is cheerful and immensely pleased that she has finally, after three years, lost her edema. With the disappearance of her edema, as Dr. Coleman has indicated, her serum albumin has risen. Her serum cholesterol has fallen. On the other hand, her phenolsulfonphthalein excretion has fallen to zero and she has become profoundly anemic. Her urea nitrogen has now reached levels which suggest that she has but little time ahead.

Happily, there is another course open to at least some of these individuals who revert from their nephrotic phase to a latent phase of glomerulonephritis as characterized by the presence of albuminuria alone. In (Table III) you may see a summary of the course of another patient, who six years ago presented the full-blown nephrotic picture. As you see, in 1946 his serum protein is perfectly normal. He has no nitrogen retention, he has not developed anemia, his

phenolsulfonphthalein excretion is normal, and he has no edema. He has, of course, persistent albuminuria. The only significant change that has transpired in this patient in the course of some six years is that he has developed very definite arterial hypertension. I am going to ask Dr. Seegal to discuss further the question of the course of the nephrotic phase of chronic nephritis.

Next in importance is the question of salt. As you have heard repeatedly, the sodium ion is the sinner in the production of edema, and it is logical to restrict sodium administration in the nephrotic patient. If the sodium ion is adequately restricted, preferably to less than half a Gm. per day, the patient may drink water freely because he will not, in the absence of isosthenuria,

TABLE III

PATIENT J. A., NEPHROTIC SYNDROME

Date	Edema	Albuminuria	Blood Pressure, Mm. Hg.	Hemoglobin, Gm.	Total Serum Protein, Gm. Per Cent	Serum Cholesterol, Mg. Per Cent	Serum N.P.N., Mg. Per Cent
1939–1940 incl.	+ to 0	0					
January 1941	++	++++	135/95	17.0	4.5	440	140
February 1941	+	++++	137/90	14.0	3.3	535	50
March 1941	++	+++	140/100	17.0	2.2*	585	53*
April 1941	+++	++++		11.0	2.8	704	
December 1941	0	++++		14.0	5.8	423	
January 1942	0	+++	150/100	16.0	6.1	266	30
January 1943	0	++++	135/95	16.0	6.3	281	26
April 1944	0	+++	158/120	17.0	6.4	191	34
April 1945	0	+++	145/110	17.0	7.1	281	31
April 1946	0	+++		17.1	6.0	265	30
October 1946	0	++++	180/150		6.0		30

* After acacia.

Before that I should like to review briefly the problem of therapy. You know and I know in medicine, by and large, the greater the number of "cures" the less specific is the "cure." In the nephrotic state we have innumerable measures recommended for treatment, and this may be construed as indicating that none of these methods is wholly satisfactory.

Diet is the first to be considered, and as I have said, the results of forced protein feeding have been disappointing. Beyond giving the patient enough protein to maintain nitrogen balance and to restore body protein lost, I think there is little to be said in favor of excessive (3 or more Gm. per Kg.) protein feeding and it is possible that it may increase renal damage, as suggested by Addis.

elaborate interstitial fluid which is very hypotonic. The maintenance of an essentially normal osmotic pressure is a physiological characteristic jealously guarded by the body.

The use of diuretics is, of course, of interest. There are several categories of these agents. I have already mentioned potassium, ammonium and calcium salts. They have to be given in inordinately large quantities to induce appreciable diuresis in the nephrotic state and even then the effects are usually evanescent and disappointing. The administration of urea in doses of 40 to 60 Gm. a day is at times associated with profound diuresis. The number of failures, however, raises the question of how often these results with urea are happenstances.

The mechanism of action of these diuretics has been discussed with you before.

The mercurial diuretics have a place in the treatment of nephrotic edema and are apparently innocuous in the absence of severe renal failure, but they obviously should be administered repeatedly only if they produce significant diuresis.

Thyroid extract has been employed in the treatment of the nephrotic state but with disappointing results. Pyrogenic reactions induced by the intravenous injection of typhoid vaccine have also been used to initiate diuresis. This measure is occasionally successful, but the effects are usually transient and the therapy heroic.

Hypertonic glucose has been used in the hope of withdrawing water from the interstitial compartment, increasing the plasma volume temporarily, and offering more fluid to the kidney to increase glomerular filtration. Again, the results are usually disappointing.

In view of the low osmotic pressure of the plasma, it is natural that various osmotically active substances should have been employed, and the first of these was acacia. The occasional effectiveness of this agent cannot be doubted but it is unpleasant material. At times it causes marked pyrogenic reactions and these may, at least in part, be responsible for the diuretic effect. Furthermore, acacia is often stored in the liver and in the spleen. It also may induce thrombosis in cerebral and other vessels.

Plasma has at least theoretical value in treatment. Unfortunately, even temporarily beneficial results obtained following large quantities of this material are relatively few. It must be remembered that plasma not only contains physiological salt solution but also a large amount of sodium from citrate used in its preparation.

The most recent contribution to treatment in the nephrotic state is the use of salt-free human albumin, as employed by Thorn, Armstrong and their co-workers. There are certain points which should be emphasized concerning the use of this product of plasma fractionation. First of all, it requires the intravenous administration of anywhere from 150 to 500 Gm. of human serum albumin to induce diuresis in most cases. When these massive doses of albumin are given (usually 50 Gm. daily), as much as 50 to 75 per cent of the material is excreted by the kidney. We have already indicated that heavy albuminuria probably results in the choking of the renal tubules with reabsorbed albumin. It seems possible that a very important part of the diuretic effect of serum albumin is that of effecting temporary tubular damage and thereby decreasing the reabsorption of sodium salts and water. This view receives support in the fact that diuresis in many patients takes place without a significant rise in the serum albumin level. That is to say, diuresis may not be dependent upon re-establishing the normal serum osmotic pressure, perhaps contrary to expectation. The economic factor in this treatment also deserves mention. In the process of plasma fractionation, it requires about 1,500 cc. of human blood to yield 25 Gm. of serum albumin. If 500 Gm. of albumin are required to treat one patient, 30 liters of blood or the equivalent of sixty ordinary transfusions must be employed. Furthermore, there is no assurance that the diuresis induced will be permanent and it seems improbable that this therapy fundamentally modifies the course of the underlying nephritis beneficially.

I am going to ask Dr. David Seegal, who with his group at the Goldwater Memorial and the Babies Hospital has had a wide experience with chronic nephritis, to discuss certain aspects of the nephrotic state.

DR. SEEGAL: Dr. Loeb has asked me to comment on certain data which we have accumulated. We agree that there are some patients who emerge from the neph-

rotic phase of glomerulonephritis and do not immediately enter the pre-uremic stage. Dr. Deming has reviewed the case histories of three of our patients who have returned to work following a prolonged nephrotic phase. The edematous periods of these patients were six months, one year, and two and one-half years. Since diuresis they have been followed for seven, five, and three years without any symptoms of nephrosis but in each case with persistent albuminuria and microscopic hematuria. It is thus seen that some individuals may pass through a severe nephrotic phase in the course of chronic glomerulonephritis and subsequently experience a reasonably normal life for as long as seven years.

We have come to believe that the nephrotic phase develops in the majority of patients with glomerulonephritis if the disease is prolonged. The frequency of this episode has led Dr. Bloom to emphasize its usefulness as a diagnostic criterion in defining the nature of the lesion in patients with renal failure.

I would like to raise several questions which would be brought up by Dr. Lyttle, with whom we were associated at the Babies Hospital. Dr. Lyttle has had experience with a large series of children with glomerulonephritis. He tells us that the large majority of children with acute nephritis recover completely. A few die of myocardial failure, severe hypertension with cerebral edema, or infection. When the disease in childhood progresses into the subacute and chronic stage, he has never seen the full nephrotic syndrome develop; that is to say, that children in the hospital with a nephrotic syndrome do not present a history of antecedent, clinically recognized acute glomerulonephritis.

Dr. Lyttle and I studied some of the immune reactions to the Group A hemolytic streptococcus in patients during various stages of glomerulonephritis. One of our control groups consisted of children diagnosed as nephrosis. In contrast to the values found in normal individuals, thirty-six of thirty-eight children observed early in the course of nephrosis had abnormally low antistreptolysin titers; in the great majority, the value was less than 10 units. With remissions of the disease, when edema diminished and the serum albumin rose, the antistreptolysin titer returned to normal levels in fifteen of twenty patients. Eight relapses of nephrosis were observed in five patients with quiescent nephrosis. In seven of these relapses there was an associated drop in antistreptolysin titer from the normal to the abnormally low value. Despite the fact that the base line antistreptolysin titer is less than 10 units in these children with nephrosis, Group A hemolytic streptococcus infections produce a rise in antistreptolysin titer comparable to that expected in a normal child following a similar infection.

Studies of the immune response of adults with chronic glomerulonephritis by Dr. Earle in this clinic have shown that the base line antistreptolysin titer in the nephrotic phase is lower than that found in the same individuals in the non-edematous state. However, it is unusual to observe the low antistreptolysin titer values of nephrosis in the adult nephrotic phase. If we continue in this line of immunological thought, we might add that we have been puzzled by the rarity of the occurrence of pneumococcic peritonitis in our adult nephritics with ascites in contrast to the frequency of this episode in the nephrosis of children.

We hope that Dr. Kendall will comment on these immune reactions. Is there a possibility that the low antistreptolysin titers are related to a diminution in the gamma globulin content of the serum in nephrosis and the nephrotic phase of glomerulonephritis?

DR. KENDALL: There is no answer from our present information but it is a possibility.

DR. LOEB: I would also like to ask this question: If we are right in our assumption that serum albumin in the nephrotic state is not synthesized normally, and there are means at our disposal today by which that can be determined, is it possible also that the antistreptolysin is not synthesized normally?

DR. KENDALL: I think you can give certain answers to that. The fact that the antistreptolysin titer does go up following a streptococcal infection indicates that the individual does have the capacity for an immune response. The low basic antistreptolysin level in nephrotic patients may result from increased excretion of the globulin through the kidneys or from increased breakdown.

DOCTOR: The frequency of occurrence of pneumococcic infections in children with the nephrotic syndrome offers ample opportunity to study the immune response to the pneumococcus as well as to the streptococcus. Have studies been made in that direction?

DR. SEEGAL: A number of things are known about that, but the opportunity for making such studies is rapidly disappearing in naturally occurring pneumococcic infections. Since the introduction of penicillin therapy, none of these nephrotics has his pneumococcic infection long enough to evaluate immune responses. Dr. Lyttle believes that the immediate outlook for children with nephrosis is now excellent, though the development of nephritis with increasing renal insufficiency remains an ultimate hazard.

SUMMARY

The nephrotic syndrome is characterized by albuminuria, edema, hypoalbuminemia and hypercholesterolemia; frequently, it is accompanied by a depression of the basal metabolic rate. It occurs most often in the course of chronic glomerulonephritis but may exist independently, as in lipoid nephrosis. Rarely, it is associated with secondary syphilis, leptospiral infections, amyloid disease, Kimmelstiel-Wilson syndrome or nephrotoxic poisons.

The term "nephrosis" was originally applied by Müller to degenerative lesions of the kidney primarily involving the renal tubules. The nephrotic state, however, occurs also with inflammatory diseases of the kidney. Furthermore, the significance of the tubular lesion in the etiology of the syndrome is open to question for it has been quite clearly shown that, in some instances at least, the tubular change may be the result and not the cause of albuminuria. It is obvious that some disturbance of the glomerular filter or in the serum proteins must be predicated to allow for the increased supply of protein presented to the tubules.

It was originally suggested by Epstein that the low serum albumin in the nephrotic state might result solely from urinary loss of serum proteins and that edema formation could be adequately explained on the basis of the Starling hypothesis of lowered osmotic pressure in hypoalbuminemia. But there is evidence that the Epstein hypothesis does not afford a complete explanation for the formation of edema. Thus diuresis may occur spontaneously without any increase in the low serum albumin levels. Excess protein intake usually does not restore the blood level of albumin even when positive nitrogen balance is established and body protein is stored.

It is now plain that leakage of albumin through the kidneys does not alone explain the manifestations of the nephrotic state, which evidently involves much more profound metabolic disturbances. Other factors evidently are at work. There is a renal de-

fect in the handling of the sodium ion by the kidney. Adrenal cortical hormones conceivably might play a part in water and sodium balance; and the rôle of the antidiuretic hormone of the posterior pituitary gland has yet to be properly evaluated. The significance of hypercholesterolemia and lowered basal metabolic rate in the nephrotic state is not known, nor is it understood why the alpha globulins apparently are increased and the gamma globulins decreased in the blood.

Measures directed against the clinical abnormalities present in the nephrotic syndrome include diet high enough in protein to assure nitrogen balance; excessive feeding of protein accomplishes nothing more than restoration of body protein and may actually injure the renal tubules. Sodium intake is kept to less than 0.5 Gm. daily because more tends to promote edema. At this level, water may be taken freely; otherwise it, too, should be restricted. Of the diuretics, urea and mercurials are most often effective, but neither can be relied upon. Efforts to promote diuresis by increasing the osmotic pressure of the circulating plasma have been unsatisfactory. Therapy with hypertonic glucose, acacia, human plasma or serum fall into this category. Salt-free for human albumin may be highly effective but has serious limitations. Thyroid extract rarely produces diuresis. In children, intercurrent infections, particularly pneumococcic peritonitis, respond promptly to penicillin. Syphilitic nephrosis also yields rapidly to treatment with penicillin.

Prognosis depends on the underlying disease. In lipoid nephrosis and chronic glomerulonephritis the duration of the nephrotic state cannot be predicted. In the former, however, the outcome is almost uniformly good today since formerly fatal infectious complications may now be adequately handled. Patients in the nephrotic phase of chronic glomerulonephritis, however, (and these comprise by far the largest proportion of cases) still face the ultimate fate of patients with the underlying disease.

Clinico-pathological Conference

Coronary Artery Disease*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a fifty-three year old white, married farmer who entered the Barnes Hospital for the first time on February 9, 1943, complaining of abdominal pain and swelling of the ankles. The family history revealed that his mother had died of diabetes and one sister had died of an illness thought to have been tuberculosis. The patient had enjoyed excellent health with few exceptions until the onset of his present illness. He had done hard work as a farmer and had never had to limit his activity. At the age of twenty-four he had a probable Neisserian infection and for ten years he had had intermittent pain, radiating down the back of the left leg. He had consulted his family physician who told him he had "sciatica." His habits were good and his diet ample. His normal weight was 195 pounds but during the course of his illness he lost 45 pounds.

In 1940, the patient developed an easily reducible right inguinal hernia for which he wore a truss. In March, 1942, he had a sudden onset of severe pain at the site of the hernia which became irreducible. He became progressively ill and was admitted to a hospital in another community where an operation was performed. The patient was told that although the bowel had been discolored, none was removed. The hernia was repaired and recovery was uneventful. Following the operation the patient noted the onset of constipation and thereafter he had to use cathartics constantly. Several months later he began to have attacks of sharp, generalized, abdominal pain which were associated with considerable distention. During the attacks he could see and feel intestinal movement against the abdominal wall. The episodes were relieved following the passing of flatus. They bore no relation to meals or the time of day and were not accompanied by nausea, vomiting or the passage of blood in the stools. The patient found that the continual use of mineral oil and cascara diminished the severity of the attacks but he was forced to limit his diet to soft foods and liquids. Because of loss of weight and weakness, he had to stop working. Two weeks before entry to the Barnes Hospital, ankle swelling was noted and the patient became short of breath on exertion. He consulted several physicians but because his symptoms continued, he was admitted to the hospital on the Surgical Service.

At the time of entry, the temperature was 37°C., pulse 86, respirations 20, and blood pressure 120/80. The patient was a well developed but poorly nourished white male who did not appear acutely ill. The skin was loose and there was evident weight loss. The pupils reacted well to light and accommodation, and the fundi were normal. The ear drums were retracted and there was

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slight hearing loss bilaterally. The teeth were in poor repair; many cavities were present and pyorrhea was extensive. The throat appeared normal. The chest was barrel-shaped and resonant to percussion. There were no abnormal findings on auscultation. Aside from distant sounds, examination of the heart was not remarkable. The abdomen was distended and the umbilicus was almost obliterated. Peristaltic waves were observed to move from left to right. There was marked tympany to percussion, and on auscultation, peristaltic sounds were heard at intervals. Questionable signs of fluid were noted in the flanks; no masses were felt. A long, well healed scar was present in the right inguinal region and the inguinal rings were lax on both sides. Transmitted impulses were felt bilaterally when the patient coughed. The right testis was larger than the left. The prostate was enlarged and boggy. Questionable early clubbing of the fingers was noted. There was pitting edema over the ankles and the feet. Neurologic examination was within normal limits.

The laboratory studies were as follows: Blood count: red cells, 4,160,000; hemoglobin, 11.4 Gm.; white cells, 12,800; differential count: eosinophiles, 1 per cent; stab forms, 2 per cent; segmented forms, 56 per cent; lymphocytes, 32 per cent; monocytes, 9 per cent. Urinalysis: negative. Stool: guaiac negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 33 mg. per cent; total protein, 6.2 Gm. per cent; albumin, 3.6 Gm. per cent; globulin, 2.6 Gm. per cent; hematocrit, 40 per cent. Blood indices: mean corpuscular volume, 85 cubic micra; mean corpuscular hemoglobin, 29.5 gamma gamma; mean corpuscular hemoglobin concentration, 35 per cent. Electrocardiogram: T wave low in leads I, II, III; slurring and notching in all leads. Impression; myocardial damage.

Shortly after admission the patient was fluoroscoped. The heart was found to be transverse in position; the aorta was widened and lengthened and the diaphragms moved well. A subsequent stool examination was reported as guaiac positive. Proctoscopy was performed and a reddened mucosa without any gross lesions was seen. The patient was prepared for laparotomy by decompression with a Miller-Abbott tube; he received blood and plasma transfusions and was given sulfasuxidine by mouth.

On February 25, 1943, a laparotomy was performed. The omentum was found to be pulled over and was adherent to the splenic flexure of the colon. This attachment formed a band producing a hiatus into which the entire small intestine, with the exception of the duodenum, had herniated. The adhesions were divided and immediately thereafter the transverse colon and sigmoid were seen to fill with gas. Eight inches from the ileocecal valve the ileum was found to be stenosed by an annular fibrous constriction within its wall, the lumen being less than 0.5 cm. in diameter. An ileo-ileostomy was performed.

The postoperative course was uneventful until March 3, 1943, when it was noted that the patient's left leg was swollen. A diagnosis of thrombophlebitis was made and a left lumbar paravertebral block was performed; it had little effect on the swelling. Several days later the patient became short of breath and his pulse rose to 140; edema of the legs, thighs and sacrum was observed. The neck veins were distended. The heart was enlarged to percussion and the sounds were distant and of poor quality. The blood pressure fell to 110/95 and a few râles were heard at the lung bases. The patient was seen by a medical consultant and a diagnosis of myocardial infarction was made; it was confirmed by repeated electrocardiograms. The patient was treated with digitalis, a low salt diet, absolute bed rest, and

mercurial diuretics, and over a period of several weeks gradually improved. The pulse rate returned to normal, the sedimentation rate, which had risen during the acute episode, likewise returned to normal, and the patient became symptom-free. After five weeks of bed rest he was allowed to resume activity gradually, and was discharged on a maintenance dose of 0.1 Gm. of digitalis daily, a salt-free diet, and advised to limit his activity. He was instructed to return for follow-up examination.

Following discharge from the hospital, the patient continued to improve and he was able to do moderate labor on his farm without symptoms. He took 0.1 Gm. of digitalis a day and noted dyspnea only on rather marked exertion.

Six weeks before his second hospital admission he began to experience slight nausea, fleeting abdominal pain, weakness, increasing shortness of breath and increasing fatigue and palpitation. He developed slight ankle edema, more on the right. His appetite became poor, his abdomen increased in size and he gained approximately ten pounds. He was given ammonium chloride by his physician with some diminution in the amount of edema. The digitalis dosage was tripled but the major symptoms persisted and he was admitted to the hospital on the Medical Service on August 31, 1946.

Physical examination on entry revealed the temperature to be 37.4°C., pulse 80, respirations 28, and blood pressure 120/88. The patient was well developed and well nourished. He was dyspneic and moderately orthopneic; the lips were slightly cyanotic. Examination of the fundi revealed only narrowing of the arterioles. The neck veins were markedly engorged. Over the right lower lobe posteriorly, tactile fremitus was absent, breath sounds were diminished and there was flatness to percussion. Above this area and also at the left base posteriorly, moist râles were heard. The heart was enlarged 15 cm. to the left of the midsternal line in the fifth left interspace; dullness extended 6 cm. to the right. The rhythm was totally irregular and there was a pulse deficit of 8. The sounds were faint. A soft systolic murmur could be heard over the entire precordium. The liver edge was moderately tender and was felt 10 cm. below the right costal margin. Signs of ascites were elicited on examination of the abdomen. The peripheral arteries were thickened; 1+ pitting edema of the extremities was present and a small easily reducible right inguinal hernia was noted.

The laboratory studies were as follows: Blood count: red cells, 5,080,000; hemoglobin, 14 Gm.; white cells, 13,750; differential count: juvenile forms, 4 per cent; stab forms, 4 per cent; segmented forms, 67 per cent; lymphocytes, 19 per cent; monocytes, 6 per cent. Urinalysis: negative except for a rare granular cast in the centrifuged sediment. Venous pressure: 230 mm. H_2O. Circulation time: arm to tongue with Decholin, 40 seconds; arm to lung with paraldehyde, 18 seconds. Non-protein nitrogen: 23 mg. per cent. Roentgenogram of the chest: "There is considerable enlargement of the cardiac silhouette. The aorta is lengthened. The hilar shadows are prominent and the lung markings are coarse. There is partial obliteration of the right costophrenic angle with fluid." Electrocardiogram: low voltage in leads I, II, III; marked notching of the QRS complex; T waves low upright in leads I, II and III; occasional ventricular premature contraction.

The patient was placed in an oxygen tent on admission and a regimen was ordered which included 0.1 Gm. of digitalis daily, 2 Gm. of ammonium chloride four times daily, and a salt-free diet. On the day after entry the pulse was regular at 130. Several hours later the rate had fallen to 88 with an occasional ventricular premature con-

traction. The heart sounds were of poorer quality than on entry and a presystolic gallop rhythm appeared. Respiratory difficulty increased during the day and cyanosis became more prominent. On the evening of the second day the patient complained of substernal oppression and his dyspnea increased. The heart sounds at that time were faint and the rhythm was regular. No râles were heard on auscultation of the lungs. Fifteen minutes after these findings were noted, the patient gasped and died immediately.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: Although the main diagnostic problem in this case concerns the nature of the cardiac disease, three phases of the patient's illness are worthy of comment: first, the identity of the gastrointestinal lesion which led to the first admission; second, the postoperative complication which was interpreted as cardiac in origin; and finally, the nature of the terminal episode. Dr. Kenamore, would you comment on the lesion described in the terminal ileum at the time of the laparatomy?

DR. BRUCE D. KENAMORE: I believe the lesion was benign for the patient lived three years after the operation; malignancies of the small bowel lead to death in a shorter period of time. Of the benign lesions, either regional ileitis or a non-malignant neoplasm must be considered.

DR. WOOD: The lesion was described as being constrictive. May a tumor cause such constriction?

DR. KENAMORE: Yes. Fibromatous tumors of the small intestine, in particular, may impinge on the lumen and give rise to intestinal obstruction.

DR. WOOD: Would you comment on the time relationships in this case? The patient's symptoms all developed after his operation for hernia. Do you think it possible that, as a result of the first operation, pathologic changes occurred which ultimately led to the second operation?

DR. KENAMORE: It is conceivable that postoperative adhesions caused intestinal obstruction but that diagnosis seems less likely to me than the first two I mentioned. Regional ileitis often involves a larger portion of the small intestine than was described here and the lesions are frequently multiple.

DR. CARL V. MOORE: I have seen annular constrictions of the small intestine at postmortem examination for which there was no definite explanation. They were thought to be due to injury or infection but were not typical of regional ileitis.

DR. PALMER H. FUTCHER: Dr. Moore, would you comment on the etiology of regional ileitis?

DR. ROBERT A. MOORE: There is no proven cause of regional ileitis; much of the evidence suggests that the process is associated with lymphatic obstruction.

DR. WOOD: Let us now consider the nature of the postoperative episode. The patient exhibited many of the signs of congestive heart failure. Edema was particularly prominent in the left leg and there was dullness to percussion at the right lung base but at no time did the patient cough up blood. Dr. Smith, would you comment on these findings?

DR. JOHN R. SMITH: In all probability there was a diminution or obstruction of the coronary flow resulting in a myocardial infarction with associated cardiac failure. The fact that the edema was confined to the left leg is not too remarkable; not infrequently patients in congestive failure have edema only in one leg and in such instances it is usually the left which is involved.

DR. WOOD: Is coronary occlusion common following operation?

DR. SMITH: Coronary occlusion may occur following an operation, particularly in patients with arteriosclerotic coronary

artery disease. It has been shown that when the blood pressure falls following an operation, the coronary blood flow may be reduced to such an extent that myocardial infarction results even without complete occlusion of the lumen of an artery. Such a sequence of events might have transpired here.

DR. WOOD: Dr. Schroeder, what are your views on the occurrence of edema affecting the left leg in congestive heart failure?

DR. HENRY A. SCHROEDER: I have had an experience similar to that recounted by Dr. Smith; namely, that edema begins in the left leg in congestive heart failure. I do not know the reason although in this case the patient may have had an old healed thrombophlebitis with impaired return of venous blood from that extremity.

DR. WOOD: In my experience unilateral edema is rather rare in congestive heart failure.

DR. SMITH: I would alter my statement and say that edema is often more intense in the left leg, though usually present in both.

DR. SCHROEDER: The clinicians who took care of this patient must have postulated that he had a deep pelvic thrombophlebitis since they did a left lumbar paravertebral block. Thrombophlebitis with a pulmonary embolism must also be considered.

DR. WOOD: Is it possible to differentiate pulmonary infarction from myocardial infarction on the basis of electrocardiographic changes?

DR. EDWARD MASSIE: The electrocardiograms in this case favor the diagnosis of myocardial infarction.

DR. WOOD: Would you discuss the tracings, Dr. Massie?

DR. MASSIE: In the first tracing, taken in 1943, the voltage was low in leads I, II and III and there was a sinus tachycardia. On deep breathing the QRS segment became upright in lead III. The T wave in lead I was low but upright and that combined with the low voltage led to the interpretation of myocardial damage. An electrocardiogram several days later showed definite changes; the voltage was still low but the T wave in lead I had become isoelectric, and a definite Q wave appeared in leads CF_2 and CF_4. These changes strongly suggest a recent myocardial infarction. In the third electrocardiogram the changes were even more indicative of myocardial infarction for the S-T segment in lead IV became elevated and the rate increased to approximately 140. The next tracing showed T_2 becoming upright, T_1 isoelectric or diphasic, and a Q wave in lead I. The other leads were approximately as before. In the final record S-T_1 was rounded, T_1 inverted, T_2 less upright, and there was rounding and dipping of the S-T segment in CF_4. These changes are indicative of an acute myocardial infarction. The changes in pulmonary infarction may be somewhat similar but they are usually more precipitous.

DR. WOOD: This patient had no pain. How frequent is myocardial infarction without pain?

DR. MASSIE: Frequently patients are seen who have an abnormal electrocardiogram as, for example, indicated by the finding of left bundle branch block. In reviewing the history no episode compatible with coronary occlusion can be found but statistically most of these patients have had one. The state of clarity of the patient's sensorium is important in this regard. An ambulatory patient is usually aware of a coronary occlusion but in this patient, whose infarction occurred postoperatively, it is possible that he had not sufficiently recovered from the operative procedure to detect the pain incident to infarction.

DR. WOOD: This patient had a blood pressure of 110 over 95 and therefore a pulse pressure of only 15. Would you comment on this finding, Dr. Massie?

DR. MASSIE: Such a pulse pressure is quite low and difficult to interpret in this case, particularly if borne out by subsequent readings. A plausible explanation is that the patient's diastolic pressure was usually about 95 and that his systolic pressure fell postoperatively because of the coronary occlusion.

DR. SCHROEDER: A low pulse pressure is seen not infrequently when the cardiac output diminishes following myocardial infarction. The elevated diastolic pressure suggests generalized vasoconstriction resulting from a lowered cardiac output, anoxia and a state of impending shock.

DR. WOOD: Then you believe that this blood pressure is quite consistent with myocardial infarction?

DR. SCHROEDER: As a matter of fact, I believe it to be fairly characteristic of a severe infarction.

DR. WOOD: The general consensus of opinion seems to favor a myocardial infarction for the postoperative episode. Are there any other comments?

DR. C. V. MOORE: Frequently cases of myocardial infarction with associated cardiac failure in which digitalis is used progress to a fatal termination, and it is always pointed out that digitalis may have been toxic and thus detrimental in such instances. It should be mentioned, therefore, that this patient, although he had a myocardial infarction, apparently tolerated digitalis very well.

DR. WOOD: Dr. Smith, would you have given this patient digitalis with these clinical findings and a tentative diagnosis of myocardial infarction?

DR. SMITH: As a result of recent investigations, carried out in our laboratory at the suggestion of Dr. Schroeder, I have come to the conclusion that digitalis should be avoided in cases of myocardial infarction with failure unless the cardiac insufficiency is extreme, and then digitalis should be given with great caution.

DR. SCHROEDER: I agree with Dr. Smith.

DR. C. V. MOORE: I would have withheld digitalis in this instance but I do believe that there are a large number of patients in similar circumstances who tolerate digitalis well.

DR. SCHROEDER: I believe that, under such circumstances as these, the patient should be put to bed, kept absolutely quiet and should be given oxygen. When there is necrosis of cardiac muscle, irritable foci are set up at the slightest provocation. Furthermore, this tendency is exaggerated by the coronary spasm and anoxia. To give a drug which is a cardiac stimulant and also a myocardial irritant seems to me to be unwise.

DR. WOOD: Dr. Smith, do you think that the episode which terminated this patient's life was a second myocardial infarction?

DR. SMITH: Yes, it may well have been. However, it is possible that there was such a degree of coronary arteriosclerosis that there was myocardial insufficiency without infarction.

DR. WOOD: What is your feeling on this point, Dr. Massie?

DR. MASSIE: I believe coronary insufficiency without a fresh myocardial infarction was the most likely cause of the terminal episode, but there is not sufficient evidence to enable one to be dogmatic as to the cause of death.

DR. SMITH: A pulmonary infarction due either to an embolus or a thrombosis of the pulmonary artery must be considered, for the patient had a sudden fall in the pulse rate and became cyanotic and very dyspneic.

DR. SCHROEDER: I should like to suggest that digitalis intoxication may have led to the patient's exitus.

DR. WOOD: That is a good suggestion. The patient's digitalis dose had been doubled or trebled before he entered this

hospital. When he was admitted, his pulse was slow and totally irregular. He subsequently had a bout of tachycardia with possible auricular flutter which reverted eventually to a normal rhythm.

DR. SCHROEDER: Two-tenths of a Gm. of digitalis daily, which was the dose this man was taking, is usually tolerated by most patients but on some occasions it may give rise to toxicity.

DR. WOOD: Are there any other suggestions?

DR. MASSIE: A mural thrombus with detachment and escape into the pulmonary circulation may have led to a pulmonary infarction.

DR. MICHAEL M. KARL: Is it postulated that the increase in the patient's heart size was due to myocardial insufficiency?

DR. SCHROEDER: If the coronary arteries are narrowed and the myocardial muscle is damaged, the heart may be greatly dilated.

DR. WOOD: It is often stressed in text books that in arteriosclerotic coronary artery disease the heart is usually small. I believe, however, that Dr. Schroeder's statement is correct. Would you agree with it, Dr. Moore, from a pathologic standpoint?

DR. R. A. MOORE: In certain cases of coronary arteriosclerosis, dilatation is seen and may actually go on to hypertrophy.

DR. WOOD: In summary, it may be said from the present discussion that the staff favors the diagnosis of a benign lesion in the ileum. Either tumor or scarring resulting from previous ileitis may have caused the stricture described at operation. The illness in the postoperative period was probably a myocardial infarction and the terminal illness appeared to be due to coronary insufficiency with congestive heart failure possibly precipitated by a fresh myocardial infarction. Pulmonary infarction remains a possibility and digitalis intoxication cannot be ruled out.

Clinical Diagnosis: Benign stricture of the ileum; arteriosclerotic coronary artery disease with old and possibly recent myocardial infarction; cardiac insufficiency; ?pulmonary infarction, and ?digitalis intoxication.

PATHOLOGIC DISCUSSION

DR. OSCAR N. RAMBO: At autopsy the major findings were limited to the thorax. There were 1,700 cc. of amber fluid in the right pleural cavity and 500 cc. in the left pleural cavity. Part of the pleural space about the upper lobe of the right lung was obliterated by fibrous bands. The pericardial fluid was clear and of normal volume. *In situ*, the heart was greatly dilated and of flabby consistency; the transverse diameter was increased. On the epicardial surface there were several smooth, translucent areas with slight fibrous thickening. Beginning at the apical incisure and capping the apex of the left ventricle there was an area of softening 4 cm. in diameter. In this region the myocardium was only 5 mm. thick and was white and fibrous. Another elongated area of softening was found adjacent to the interventricular sulcus posteriorly.

On opening the heart the epicardium about the apex of the left ventricle was white, thick and fibrous. There was fibrous thickening of the anterior leaflet of the mitral valve and of the bases of the aortic cusps, the latter to such a degree that they projected slightly into the lumen of the valve. Examination of the coronary arteries showed normal ostia and yellow, elevated, fibrous plaques in the intima. At a point 23 mm. from the ostium, the lumen of the anterior descending branch of the left coronary artery was almost completely filled by an adherent, grayish-white, firm mass which extended for 10 mm. Thirty mm. from its ostium the lumen of the circumflex branch also appeared to be occluded by a soft, homogeneous, but adherent, reddish-gray mass. The lumen of the

right coronary artery was completely occluded 23 mm. from the ostium by a thrombus which was dark red and partially organized. In the right atrial appendage there was a firm, friable and laminated grayish-red mass which was organized and adherent. It measured 2 by 2 cm.

The kidneys were slightly enlarged, the right weighing 175 Gm. and the left 210 Gm. The surfaces were finely granular and the pyramids, on section, were dark purple in color. Examination of the site of the intestinal anastomosis showed no evidence of tumor. The anastomosis was 31 cm. proximal to the ileocecal valve and the stoma was 6 cm. in diameter. The prostate measured 43 by 35 by 38 mm. The cut surface presented bulging, yellow-white, translucent, nodular areas 5 to 10 mm. in diameter. There were adhesions between the spermatic cord and the right inguinal canal.

DR. R. A. MOORE: From a gross standpoint the findings constitute a fairly characteristic example of advanced coronary arteriosclerosis as evidenced by occlusion of the left descending, the left circumflex and the right coronary arteries. Thus the major part of the blood supply to the myocardium had been interfered with. In addition, there was an old infarct at the apex of the left ventricle and a more recent infarct in the posterior wall of the left ventricle.

Turning to the microscopic sections, Figure 1 shows a cross section of the left coronary artery. The lumen is filled with a mass of tissue containing vascular spaces and represents a completely recanalized thrombus. Figure 2 lends support to the fact that the occlusion was due to the recanalized thrombus rather than to an arteriosclerotic plaque for numerous macrophages filled with hemosiderin pigment are seen; these are generally assumed to be evidence that red cells had been present.

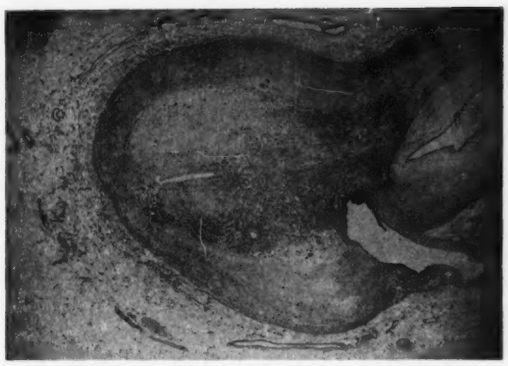

FIG. 1. Cross section of the left coronary artery showing recanalized thrombus in the lumen.

In the walls of the recanalized channels smooth muscle may be noted. The next section (Fig. 3) is taken from the left ventricular wall near the apex. There is almost total destruction so that only a few bundles of muscle fibers remain. The infarct is old, probably of months' duration. Figure 4 shows an area through an old scar. All evidence of myocardial structure has been removed and only a few blood vessels remain in the fibrous tissue. In Figure 5 a section of the right coronary artery is seen; it shows a typical arteriosclerotic plaque in the wall. The lumen is occluded by a very recent thrombus about which there is no organization; it has, therefore, been present for only a few days. In Figure 6 a papillary muscle of the mitral valve shows evidence of acute infarction adjacent to an area of old infarction. There is considerable cellular infiltration and although the infarct is not as old as the one demonstrated previously, there are other changes in the muscle which are of a duration of twenty-four to forty-eight hours. Thus there is evidence of at least two changes; first, an old infarct of months' duration and second, one which had occurred only a short time before death. Figure 7 is taken through the right atrial wall at the site of infarction. The thrombus found in the atrial appendage was typical of those not infrequently observed at the site of an old infarction.

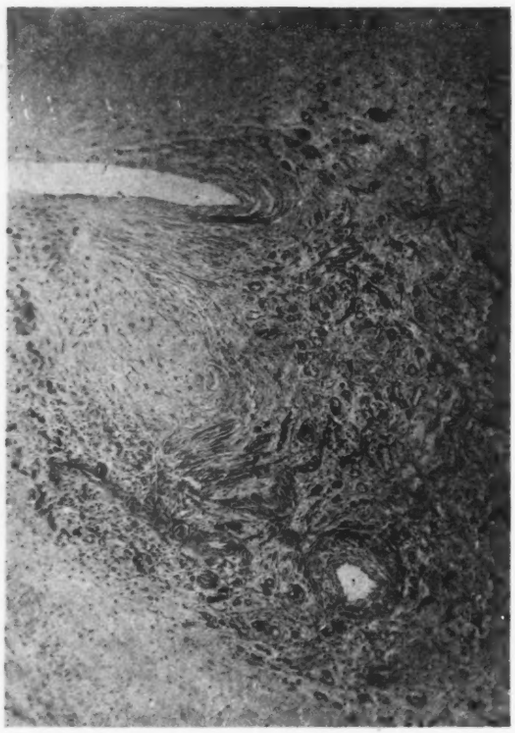

FIG. 2. Higher power view of the thrombus seen in Figure 1, showing numerous macrophages filled with hemosiderin.

In a section of the kidney (Fig. 8) there are the changes of minimal arteriolar nephrosclerosis. The blood vessels are slightly thickened and the basement membrane of the glomerular capillaries is thickened but there is no significant increase in the amount of connective tissue. There is no evidence of a chronic destructive renal lesion. The prostate exhibited the changes of nodular hyperplasia.

In attempting to correlate the clinical and pathologic findings, let us consider the history briefly. No lesion at autopsy was found which could be related to the Neisserian infection which the patient had in his youth. The right inguinal hernia resulted in adhesions between the cord and the inguinal canal on that side. These were broken with some difficulty. At the time of the laparotomy the omentum was found to be pulled over to the splenic flexure of the colon. The capsule of the spleen was thickened and there were adhesions between the splenic capsule and the diaphragm—a perisplenitis. The ileum was stenosed by an annular fibrous constriction within the wall, but at autopsy the only finding was an ileo-ileostomy with a stoma which was obviously functioning well. There was no pathologic change to indicate the nature of the original lesion. Although the left leg was more edematous than the right, the left common iliac and left external iliac veins were not the site of thrombophlebitis.

The anterior myocardial infarction was of an age consistent with the patient's episode in the postoperative period. The cardiac failure may be correlated with findings indicating chronic passive congestion of the viscera. The heart, which weighed 550 Gm., was unusually dilated; the soft systolic murmur which was heard over the precordium was probably caused by thickening at the base of the aortic valve. The liver which on physical examination extended 10 cm. below the costal margin, was noted to extend down 5 cm. at the time of autopsy. The kidney showed only slight nephrosclerosis and chronic passive congestion. Thus, the clinico-pathologic correlation in this case is quite satisfactory. The pathologic anatomist cannot demonstrate digitalis intoxication with certainty, but in experimental animals and in some patients hemorrhagic foci in the myocardium are seen under such circumstances. Such a lesion was not observed here.

Pathologic Diagnosis: Arteriosclerosis of the coronary arteries, advanced; organized thrombus in the anterior descending branch of the left coronary artery; partially organized thrombus in the circumflex branch of the left coronary artery; healed infarcts of the anterior wall of the left ventricle and anterior part of the septum and of the posterior wall of the left ventricle; thrombus with beginning organization in the posterior

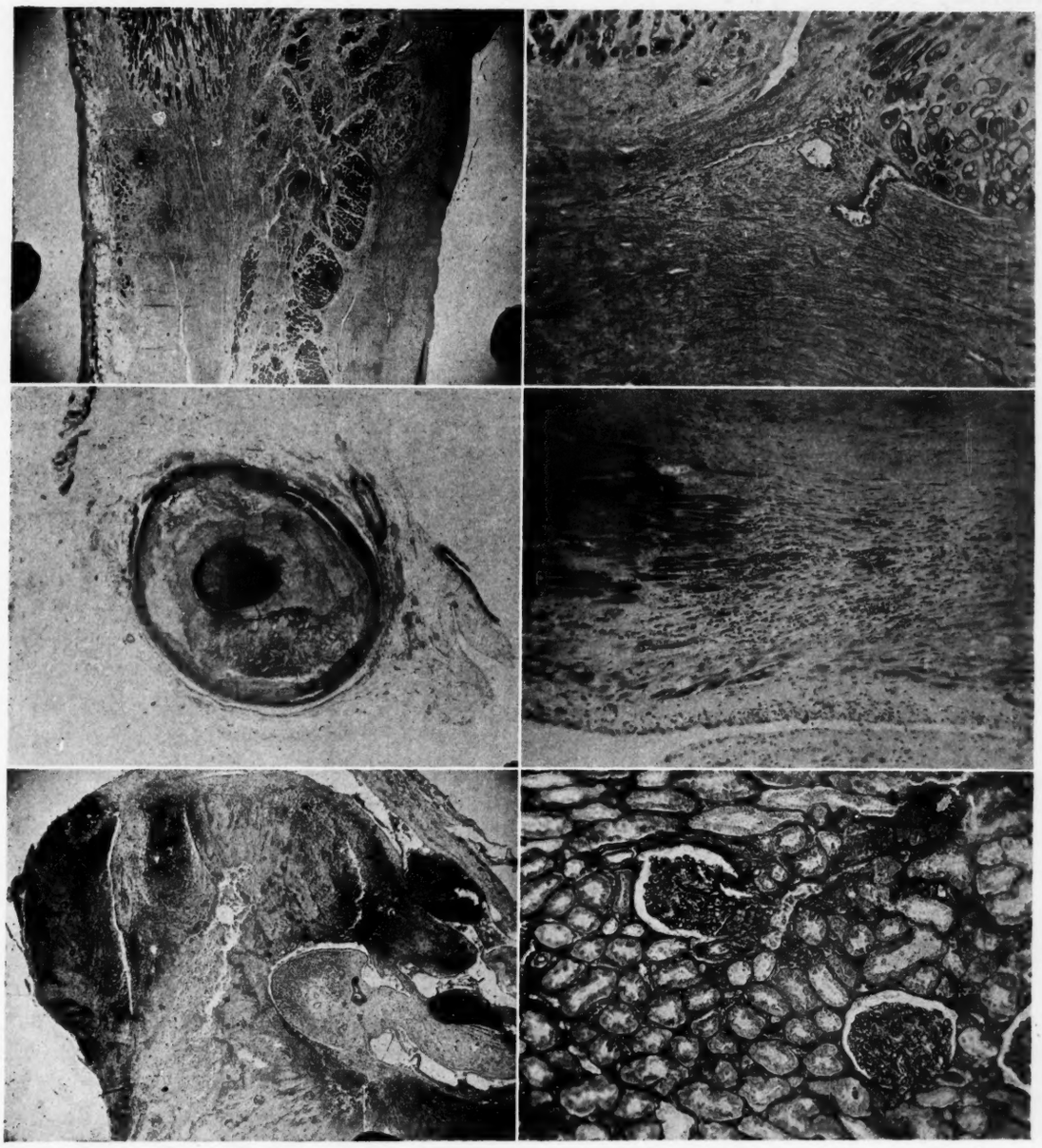

FIG. 3. Section from the left ventricular wall through the area of infarction.
FIG. 4. Another section of the myocardium through an area of old infarction.
FIG. 5. A cross section of the right coronary artery showing an arteriosclerotic plaque in the wall.
FIG. 6. Section of a papillary muscle of the mitral valve. Note the changes of both recent and old infarction.
FIG. 7. Section through the right atrial wall at the site of infarction.
FIG. 8. Section of the kidney exhibiting changes of minimal arteriolar nephrosclerosis.

descending branch of the right coronary artery; organizing infarct of the right auricular appendage; mural thromus, right atrial appendage; hypertrophy and dilatation of the heart (550 Gm.); arteriolar nephrosclerosis, slight; hydrothorax, bilateral; chronic passive congestion of the liver and kidneys, moderate; of the spleen, slight; sclerosis of the anterior leaflet of the mitral valve and cusps of the aortic valve at the bases; side-to-side anastomosis of ileum; nodular hyperplasia of prostate.

Case Report

Subcutaneous Emphysema in Vomiting of Pregnancy

HENRY M. WINANS, M.D.
DALLAS, TEXAS

SUBCUTANEOUS emphysema, usually secondary to mediastinal emphysema, has been reported as occurring in a variety of conditions, including injury, following operations, heavy lifting, straining at stool, childbirth, anesthesia with coughing, in asthma, bronchitis, after inhaling foreign bodies, in whooping cough and pneumonia, as well as spontaneously in pulmonary tuberculosis.

The present theory as to the causation is that air may reach the mediastinum and from there the subcutaneous tissues through (1) fascial planes of the neck, (2) perforation of the trachea, bronchus or esophagus, (3) from the retroperitoneal space, and (4) from the interstitial tissue of the lung. The exact mechanism of the entry of air from the air passages into the tissue is usually not known. It is assumed that the effort of coughing or straining produces a break in the continuity of the mucous membrane and that air is thus forced into the interstitial tissue whence it proceeds to the mediastinum and if sufficiently severe, into the subcutaneous tissues. When subcutaneous emphysema occurs, it does so practically always in association with air in the mediastinum. Hamman recently reviewed the literature and gave an excellent summary of present knowledge in regard to this condition.[1]

The following case is of interest because the patient developed widespread and marked subcutaneous emphysema without mediastinal emphysema and also because, although the factor which apparently produced it (vomiting of pregnancy) continued, the emphysema occurred only once.

CASE REPORT

Mrs. H., age twenty, was admitted to an Army General Hospital because of pain in the neck, shoulders and chest, together with swelling of the face, chest and back. The patient's last menstrual period was three months before admission. One month prior to admission she began to have nausea and vomiting which was not marked until five days prior to hospitalization. At this time, the nausea and vomiting were severe with considerable retching, especially in the morning. Two days before admission she developed a sudden pain in the neck during a vomiting spell. Swallowing became difficult and the pain rapidly spread over the shoulders, up into the neck and face, and was accompanied by swelling of the tissues. On admission the patient was in moderate distress, markedly dehydrated and complaining of a feeling of tightness in the throat and chest. On examination the patient presented a striking appearance with marked swelling of the face, neck, back and chest, beginning at the malar prominence on both sides of the face, extending down the neck over the shoulders as far as the deltoid insertions and to the lower rib margins, front and back. Slight cyanosis was present but there was no marked dyspnea. Definite crepitation was felt over the entire area of swelling. The lungs were normal on physical examination as was the heart. Although the air in the tissues produced crepitation on auscultation, there were no abnormal sounds arising in the mediastinum or lungs. Hamman's sign was absent. The physical ex-

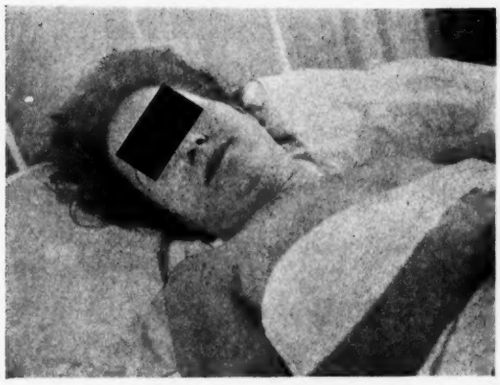

FIG. 1. Appearance of patient upon admission.

amination, otherwise, revealed nothing abnormal. Pelvic examination revealed enlargement of the uterus, consistent with pregnancy of three months' duration. There were no abnormal findings in the blood or urine. *X*-ray studies revealed the subcutaneous emphysema in the areas mentioned but no abnormal collections of air could be made out anywhere within the chest. Since the patient's condition was good and there was no respiratory embarrassment, no special treatment for the subcutaneous emphysema was given. The patient was very much relieved when an explanation for the situation was given to her. Although the nausea and vomiting continued for several days after admission to the hospital, the subcutaneous emphysema steadily decreased and was completely absent at the end of fourteen days.

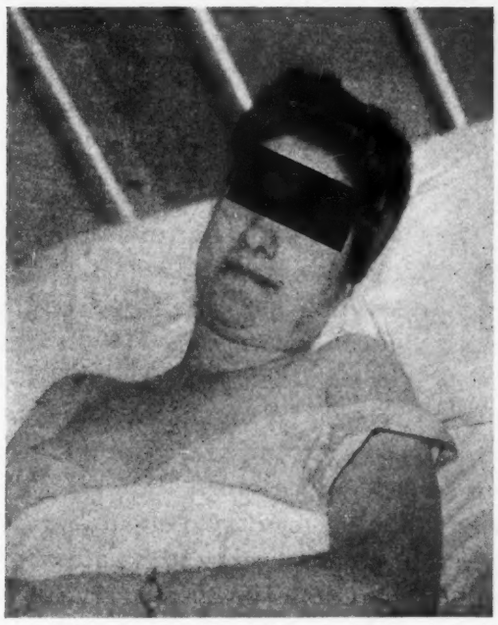

FIG. 2. Appearance ten days later.

SUMMARY

Marked and widespread subcutaneous emphysema occurred in a young woman in her first pregnancy, apparently due to the stress of vomiting. No source for the development of the emphysema could be discovered, and the condition subsided promptly in spite of the fact that the vomiting continued. This suggests the presence of some defect which, having allowed the escape of air into the subcutaneous tissues, became inoperative although the mechanism of stress continued.

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Editorial

Immunization against Influenza

Since the initial discovery of human influenza virus in 1933 by Smith, Andrewes and Laidlaw,[1] subsequently designated virus A, and the later discovery of influenza virus B in 1940 by Francis,[2] many fundamental investigations on various aspects of epidemic influenza have served to provide a sound scientific basis for the recent development of means for immunization against the natural disease. Among these investigations may be mentioned the early demonstration that the virus is pathogenic for Swiss mice; the subsequent finding that the virus can readily be cultivated in the allantoic fluid of the chick embryo; and the observation that influenza virus grown in the allantoic fluid of the chick embryo can be adsorbed by the erythrocytes of the embryo and then readily eluted from the red blood cells.[3] Equally important are a series of immunologic studies which have shown that a rise in antibody titer occurs following natural infection; that a similar increase in titer can be induced artificially by subcutaneous injection of active or inactive virus; and that mice can be immunized against an otherwise fatal infection.

Finally the development of methods for laboratory proof of diagnosis, either through recovery and identification of virus or demonstration of rise in antibody titer following recovery from infection, has served a dual purpose in further elucidating the epidemiological and clinical characteristics of influenza. First, by the use of these methods it has been possible to show the cyclic recurrence of epidemics of influenza A every two or three years and of influenza B every four to six years and to establish the fact, long suspected, that localized outbreaks of influenza and even sporadic, isolated cases occur during interepidemic periods. Secondly, it has been possible to confirm the opinion, formerly based on insecure clinical grounds, that there is a wide variation in the severity of epidemic influenza ranging from mild infections, indistinguishable clinically from other mild respiratory diseases, to severe fulminating cases reminiscent of those seen in the pandemic form of the disease. In the final analysis, as pointed out by Salk and Francis,[4] the foregoing contributions and, indeed, many others were essential prerequisites for success in devising a practical method of immunization and in demonstrating its effectiveness.

Based on the investigations briefly summarized above, the Army Epidemiological Board through its Commission on Influenza under the direction of Dr. Thomas Francis, Jr., undertook in 1941 to determine whether in fact a practical method for controlling epidemics of influenza could be developed. In 1942, Francis and Salk[5] devised a simplified method for the preparation of a concentrated and reasonably purified vaccine containing approximately equivalent amounts of influenza virus A and B. This vaccine was then demonstrated to be

[1] Smith, W., Andrewes, C. H. and Laidlaw, P. P. A virus obtained from influenza patients. *Lancet*, 2: 66, 1933.

[2] Francis, T., Jr. A new type of virus from epidemic influenza. *Science*, 92: 405, 1940.

[3] Hirst, G. K. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. *J. Exper. Med.*, 75: 47, 1942.

[4] Salk, J. E. and Francis, T., Jr. Immunization against influenza. *Ann. Int. Med.*, 25: 443, 1946.

[5] Francis, T., Jr. and Salk, J. E. A simplified procedure for the concentration and purification of influenza virus. *Science*, 96: 449, 1942.

capable not only of stimulating the production of antibodies and actively immunizing mice, but also of furnishing definite protection in human beings against experimentally induced influenza A[6] and influenza B.[7]

In the fall of 1943, with the expectation that there might be an epidemic of influenza A, a controlled study in Army Specialized Training Program units was undertaken. As a result it was determined that vaccination with a single subcutaneous injection of 1.0 cc. of a concentrated inactivated influenza vaccine given shortly before an influenza type A epidemic exerted a marked though not complete protective effect, the incidence of influenza being 3.2 times as great in the controls as in the vaccinated. There is evidence to suggest that this difference is not an adequate measure of the effectiveness of vaccination because of an apparent reduction in the attack rate in the unvaccinated controls as compared with the attack rate in groups in which none of the population had been vaccinated.[4]

Results comparable to those described above for influenza A have now been recorded[8] during the epidemic of influenza B in the late fall of 1945 with a ratio of cases in vaccinated versus unvaccinated of 1 to 9.

The fact that human resistance to influenza A and B can be greatly enhanced by vaccination with a single dose of inactivated vaccine would now appear to be well established. How frequently vaccination should be performed for the effective control of epidemics, whether means may be devised for enhancing and prolonging individual protection, and the possible effectiveness of vaccination in the face of severe pandemic influenza are problems still requiring solution.

F. G. BLAKE, M.D.

[6] FRANCIS, T., JR., SALK, J. E., PEARSON, H. E. and BROWN, P. N. Protective effect of vaccination against induced influenza A. *Proc. Soc. Exper. Biol. & Med.*, 55: 104, 1944.

[7] SALK, J. E., PEARSON, H. E., BROWN, P. N. and FRANCIS, T., JR. Protective effect of vaccination against induced influenza B. *Proc. Soc. Exper. Biol. & Med.*, 55: 106, 1944.

[8] FRANCIS, T., JR., SALK, J. E. and BRACE, W. M. Effect of vaccination against epidemic influenza B. *J. A. M. A.*, 131: 275, 1946.

Book Reviews

A NEW textbook[1] on the subject of peripheral vascular disease is a credit to the authors and the Mayo Clinic. Comprehensive, detailed, accurate and sane it is clearly phrased and thoughtfully arranged. With little doubt, it takes its place as the best single volume covering this aspect of medicine.

The three authors and eleven other contributors are all experienced in their specialties and many have carried out independent investigations in them. The tone of the volume reflects this background since it is at once authoritative yet careful to delineate known from unknown. The approach is modern, too, in the attempted correlation with physiological mechanisms. Of particular interest to the practictioner is the detailed and careful consideration given to the evaluation of the many and often useless types of therapy.

Thirty-one chapters comprise the volume. The first begins with a definition of terms; the last ends with the medicolegal aspects of these diseases. In between may be found extensive discussions of Raynaud's phenomena, the scleroderma group, thrombosis, embolism, arteriosclerosis obliterans, Buerger's disease, the arteritides, aneurysms, fistulas, vascular tumors, the range of venous abnormalities and their treatment, and a consideration of lymphedema. Each chapter subdivides the subject under consideration into its logical components so that reference to a particular point (with the aid of an excellent index) is made easier. A list of important and modern references is given at the end of each chapter. The illustrations are technically good, well chosen and aid the text. Little more could be expected from them.

Here then is a well bound and printed book which is the finest single volume yet to appear on the subject of peripheral vascular disease. F.K.H.

IN spite of wars and political upheavals, in spite of elaborate and difficult experimental procedures, in spite of the many tests required to check and re-check each new development before passing on to another, the original and painstaking discoveries of the group working under Professor Bernardo A. Houssay in Buenos Aires have stood the test of time and are unique examples of the proper and true scientific approach.

Dr. Dexter, who at one period was a collaborator in many of these studies, has done a magnificent job in his presentation and translation of the book on renal hypertension, first published in 1943.[2] Following a prologue by Prof. Houssay, one is carried step by step through the entire field of experimental hypertension and its possible relationships to hypertensive vascular disease in man. Each chapter, with detailed and critical reviews of the world-wide literature on the subject, is carefully organized, and contains a concise résumé at the end. The illustrations are many but invariably self-explanatory and clearcut.

Although one may take exception to some of the conclusions and interpretations of the authors in their attempt to place essential hypertension on a purely renal humoral basis, the reader will find no better source through which to become acquainted "with

[1] PERIPHERAL VASCULAR DISEASES. By Edgar V. Allen, Nelson W. Barker, Edgar A. Hines, Jr. with associates in the Mayo Clinic and Mayo Foundation. Pp. 871 with 386 illustrations. 7 in color. Philadelphia, 1946. W. B. Saunders Company. Price $10.00.

[2] RENAL HYPERTENSION. By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Muñoz, and Alberto C. Taquini. Translated by Lewis Dexter. Pp. 451, with 93 illustrations. Springfield, Illinois, 1946. Charles C. Thomas. Price, $6.75.

the views of those who have perhaps been responsible more than any other group for the clarification of the renal humoral pressor mechanism."

This volume is a fitting tribute to Professor Houssay and his eminent co-workers and should be obligatory reading for those individuals interested in any aspect of hypertension. G.A.P.

THIS practical book[3] is a review of peptic ulcer in which diagnosis and treatment are emphasized. There are long chapters on roentgen diagnosis, with excellent illustrations, and on differential diagnosis and medical therapy. The various theories on the etiology of ulcer are critically reviewed and the physiological mechanisms of the symptoms of the disease are discussed. An interesting chapter on experiences with the dyspeptic soldier is included, in which a reconditioning program is described which enabled 70 per cent of the patients to continue in military service.

In some of the controversial problems of treatment, the authors lean toward conservatism, and as an example, they favor delayed feeding in cases of gross hemorrhage. They also favor the simpler operative procedures in surgical treatment and state that they have frequently had disappointing results with subtotal gastrectomy.

While one may disagree at times with the opinions stated, this should not obscure the fact that this is a comprehensive, well written book which will be useful to students and practitioners. C.A.F.

THE organization and format of the second edition of this widely used text[4] is the same as the first edition. Revision of the text is largely to bring it up to date. The Lactobacillus casei factor ("folic acid") and the use of the nitrogen mustards are discussed. There is a readable account of the Rh factor. Advances in mineral and porphyrin metabolism, in large measure acquired from applications of the isotope technics, are included in a new chapter on the metabolism of the erythrocyte.

The success of the first edition is perhaps an indication of the author's achievement of objectives stated in the preface. These were "to bring together the accumulated information in the field of hematology in a systematic and orderly form, to sift the important from the less significant, to describe the newer methods which are of practical value, and to make note of those which are less essential, to outline details of differential diagnosis, to describe the indications for and methods of treatment, and to make clear as far as present knowledge permits the nature of the underlying physiologic disturbances."

The first six chapters are devoted to the development, physiology and chemistry of the formed elements and to the blood as a whole. The principles and technics of blood examinations are described in the next chapter. Other methods are discussed critically and in detail in chapters of which they form a logical part. A detailed presentation of the pathology, pathologic physiology, differential diagnosis and treatment of the anemias is arranged in the next six chapters in the classification most useful to an understanding of their causes and management. The remaining chapters are discussions of polycythemia, the purpuras, hemophilia, leukemia, tumor and tumor-like conditions involving the blood-forming organs, agranulocytosis, and infectious mononucleosis.

The text is comprehensively documented by more than 110 pages of references. The charts, tables and illustrations are, for the most part, helpful.

This book can be recommended to physicians and students as authoritative, detailed and readable. R.A.K.

[3] PEPTIC ULCER—ITS DIAGNOSIS AND TREATMENT. By I. W. Held, M.D. and A. Allen Goldbloom, M.D. Springfield, Ill., 1946. Charles C. Thomas. Price $6.50.

[4] CLINICAL HEMATOLOGY. By Maxwell M. Wintrobe, M.D. 2nd ed., 862 pp. Philadelphia, 1946. Lea and Febiger. Price $11.00.

ANTHOLOGIES are frequently best sellers so that new ones constantly appear. Here is the first entirely concerned with the doctors, nurses and patients met in contemporary fiction. Thirty five selections ranging from short stories to excerpts from longer works of thirty-four authors make up this collection.

The pieces vary widely: humor and pathos, fantasy and realism, comedy and tragedy, love and hate all are represented. One can wander through the book certain that there is something to fit the mood of the moment. While the difference in subjects is matched by the variety of style, the quality is uniformly good. The end comes reluctantly; one wishes there were more. Dr. Watson of Baker Street does not appear, nor does Dr. Arrowsmith and there was apparently no room for that memorable picture of medical student life to be found in "Of Human Bondage."

The authors are almost entirely modern. With three exceptions they are native to the English language and preponderantly American. Ernest Hemingway is the only writer with two selections in the book. Among others included are Conrad Aiken, Stephen Vincent Benet, Irvin S. Cobb, Pearl Buck, W. Somerset Maugham, Ring Lardner, Anton Chekhov, MacKinlay Kantor, Clarence Day, Jack London, A. J. Cronin, Erskine Caldwell, C. S. Forester and F. Scott Fitzgerald.

The volume is attractively bound and printed.[5] F.K.H.

[5] A TREASURY OF DOCTOR STORIES BY THE WORLD'S GREAT AUTHORS. Edited by Noah D. Fabricant, M.D. and Heinz Werner. Cloth. Pp 500. New York, 1946. Frederick Fell, Inc. Price $3.00.

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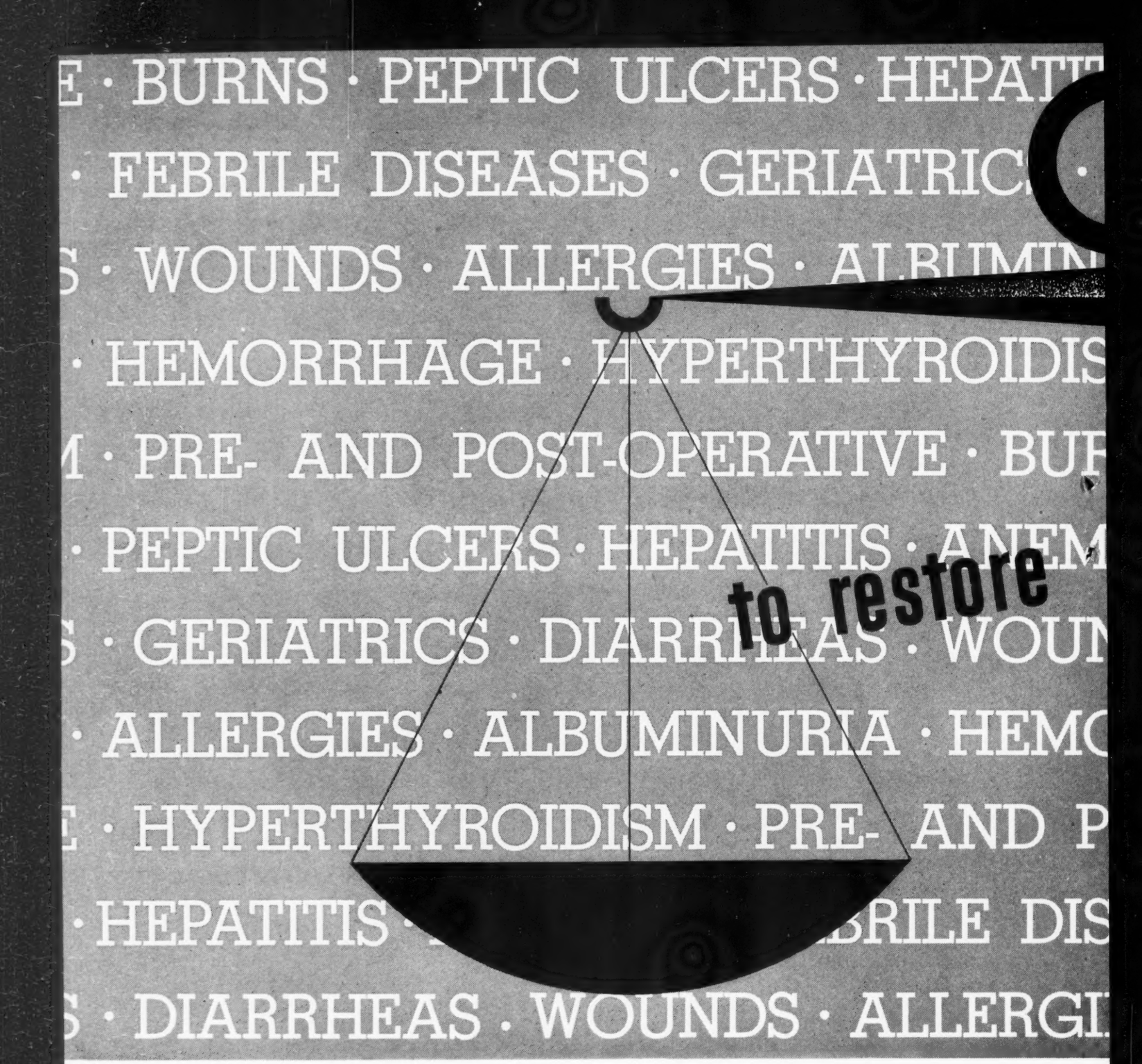

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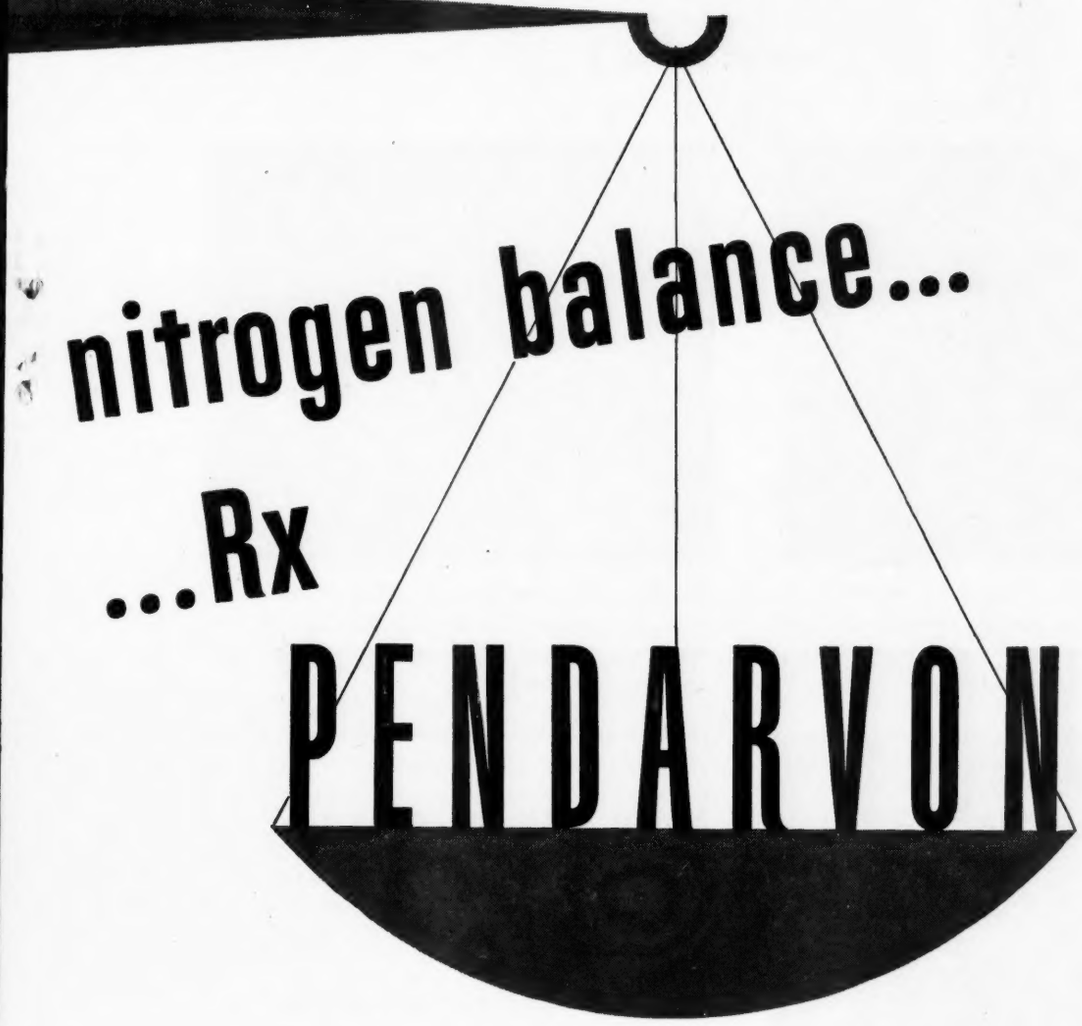

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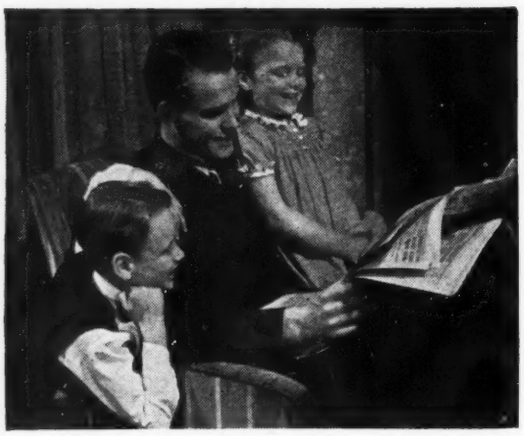

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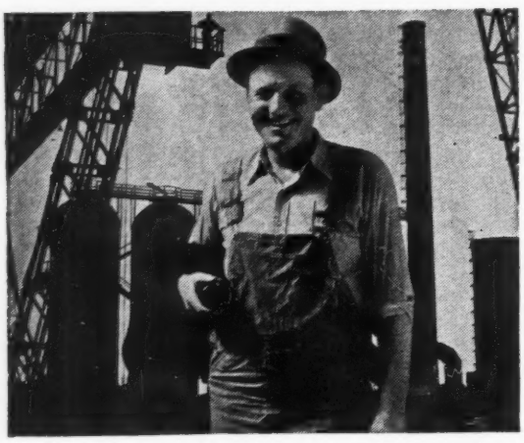

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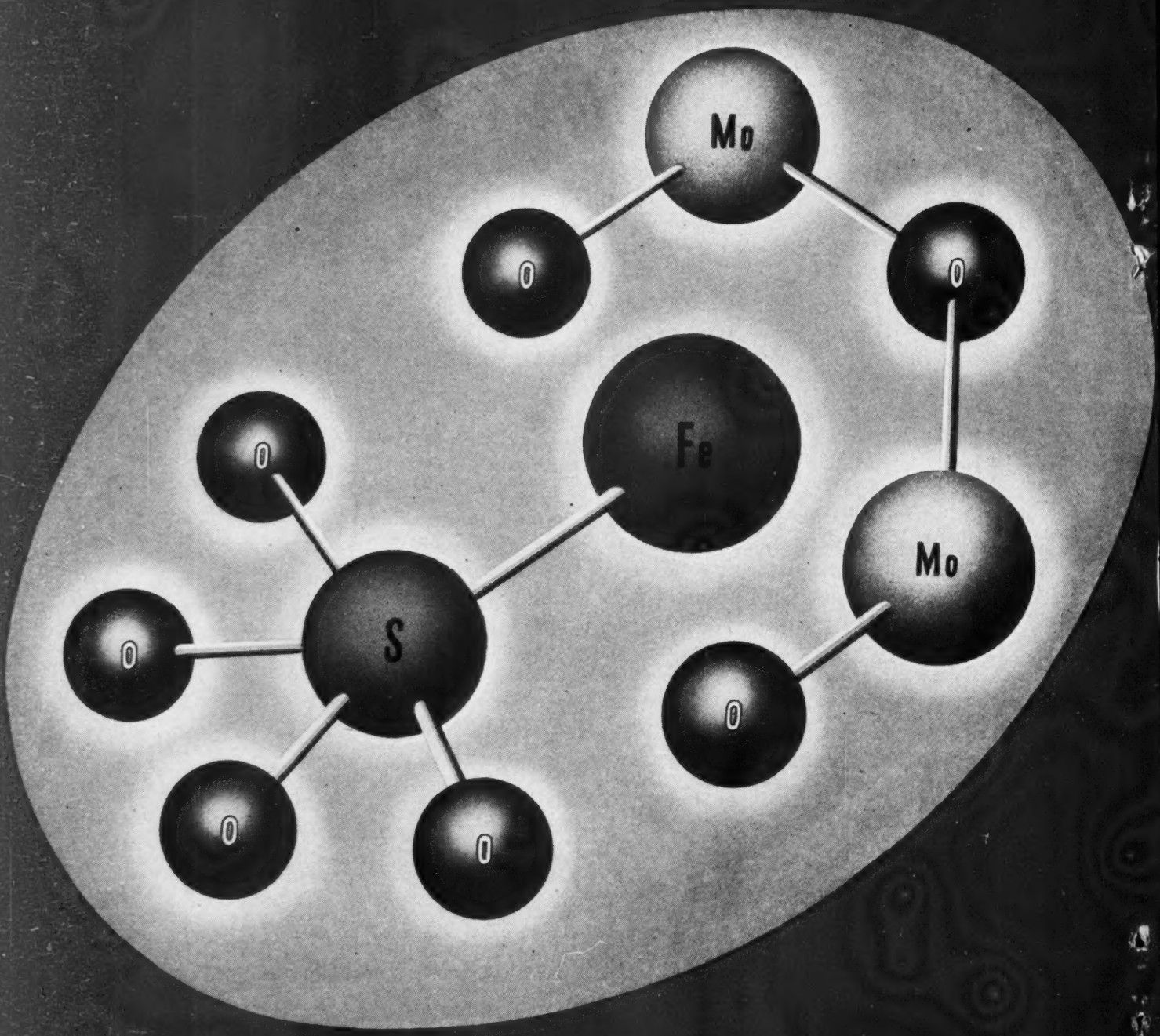

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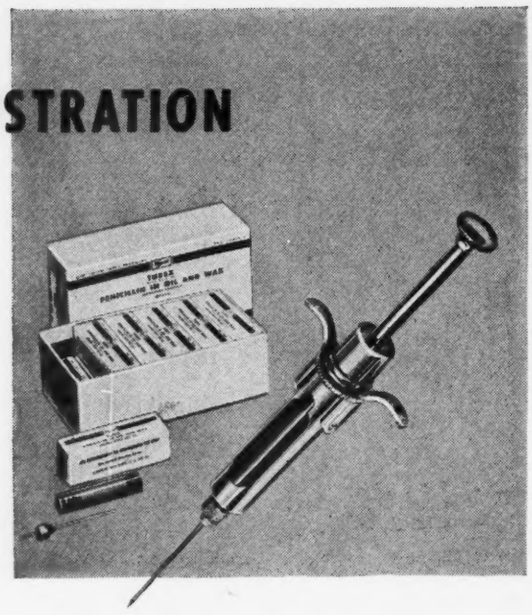

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